Gastrointestinal Tract (GIT)

(GASTROINTESTINAL DISORDERS)

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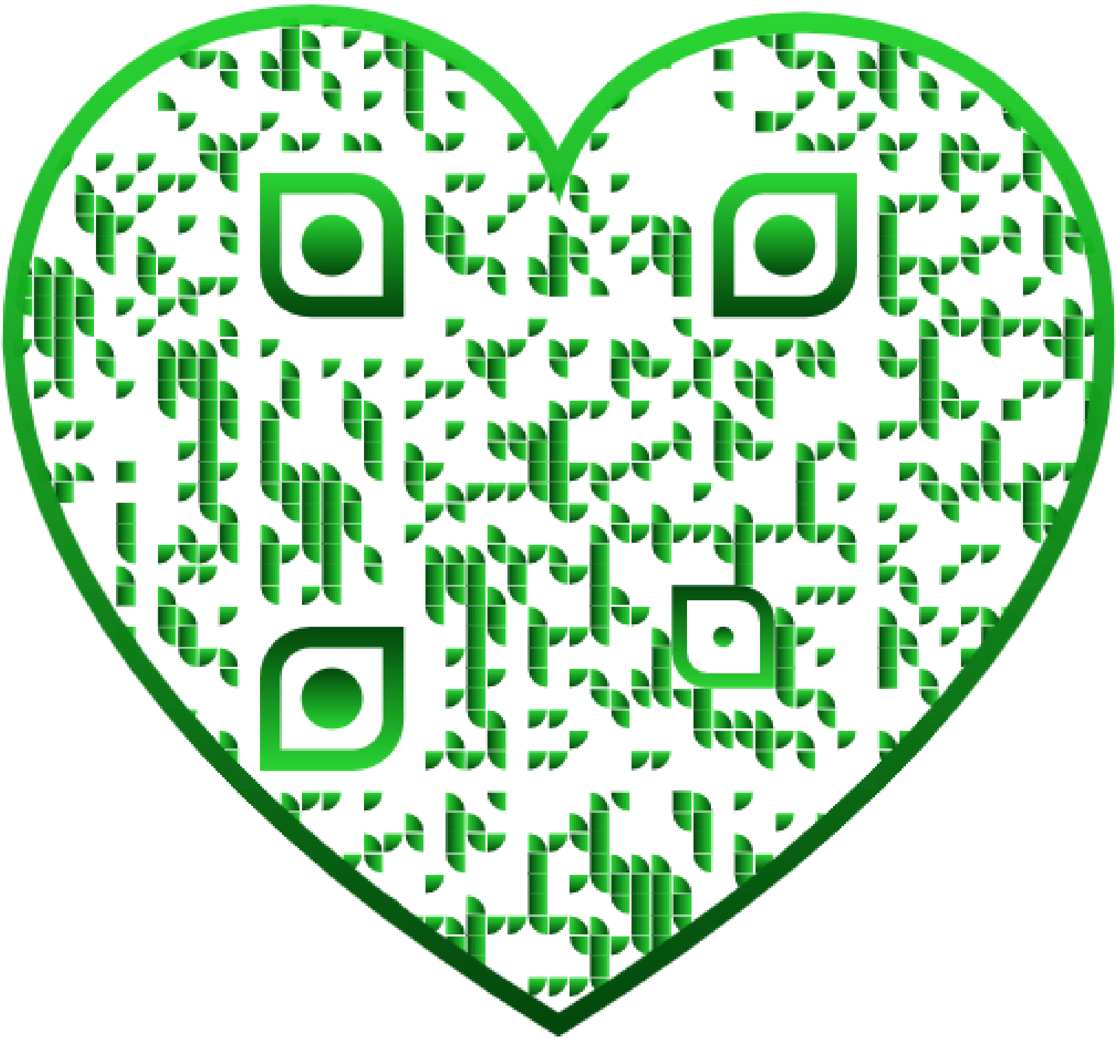
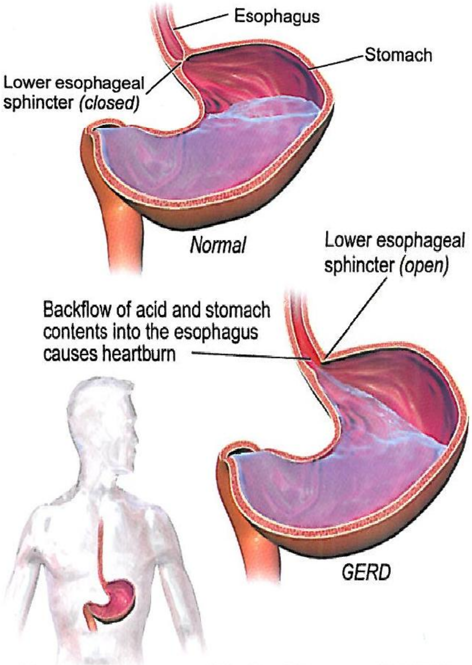
Liver diseases are separated in special chapter with kidney diseases



Gastroesophageal Reflux Disease (GERD)

➢ Overview:-

- **Gastroesophageal reflux** is the ***involuntary movement*** of **gastric contents** *to the* **esophagus.**
- **Gastroesophageal reflux** is a ***normal*** **physiologic phenomenon** *experienced intermittently* by ***most people***, *particularly* ***after*** a **meal**.
- **Gastroesophageal reflux disease** (**GERD**) occurs when the ***amount*** of **gastric juice** that ***refluxes into*** the **esophagus** *exceeds the* **normal limit**, causing **symptoms** *with* o̲r̲ *without* **complications**.
- ***Patients with*** **GERD** can exhibit *various symptoms*, both **typical** and **atypical**.
- **Typical symptoms** include **heartburn**, **regurgitation** & **belching**.
- **Atypical symptoms** include **non-cardiac chest pain**, **asthma**, **pneumonia**, **hoarseness** and **aspiration**.


Esophagus
Stomach
Lower esophageal sphincter (closed)
Normal
Lower esophageal sphincter (open)
Backflow of acid and stomach contents into the esophagus causes heartburn
GERD

Gastroesophageal Reflux Disease (GERD)

➢ Definition:-

- **GERD** ***should be defined as***; **symptoms** or **complications** ***resulting from*** the ***reflux of*** **gastric contents** *into* the **esophagus**, **oral cavity** and/or **lung**.
- **GERD** can be *further classified as*;
  - **Non-erosive reflux disease**; **Symptoms** ***without*** **erosions** on **endoscopy**.
  - **Erosive reflux disease**; **Symptoms** ***with*** **erosions** on **endoscopy**.

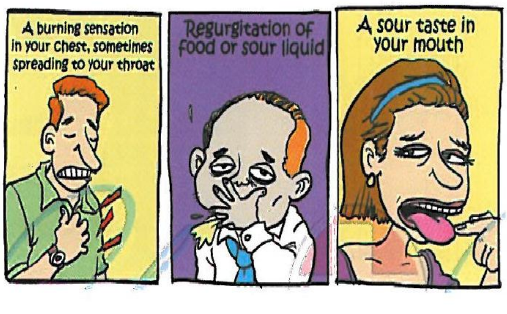
➢ Prevalence:-

- In the **Western world**; **10-20%** of the **population** are affected by **GERD** (due to Western dietary habits).
- **Heartburn** is seen in about **6%** of the **population**.
- **GERD** ***prevalence increases*** in **people** *older than* **40 years**.

➢ Symptoms:-

A) **Typical Symptoms**;

- **Heartburn** [**pyrosis**] (**Hallmark symptom**); substernal sensation of warmth or burning rising up from the abdomen that may radiate to the neck.
- **Regurgitation**; of sour or bitter liquid.
- **Belching**; acidic taste in the mouth.


A burning sensation in your chest, sometimes spreading to your throat
Regurgitation of food or sour liquid
A sour taste in your mouth

B) **Atypical Symptoms** (**Extraesophageal**);

- **Chronic cough.**
- **Asthma-like symptoms.**
- **Recurrent sore throat.**
- **Hoarseness.**
- **Dental enamel loss.**
- *Less common atypical symptoms*; **Sinusitis, pneumonia, bronchitis** and **otitis media**.

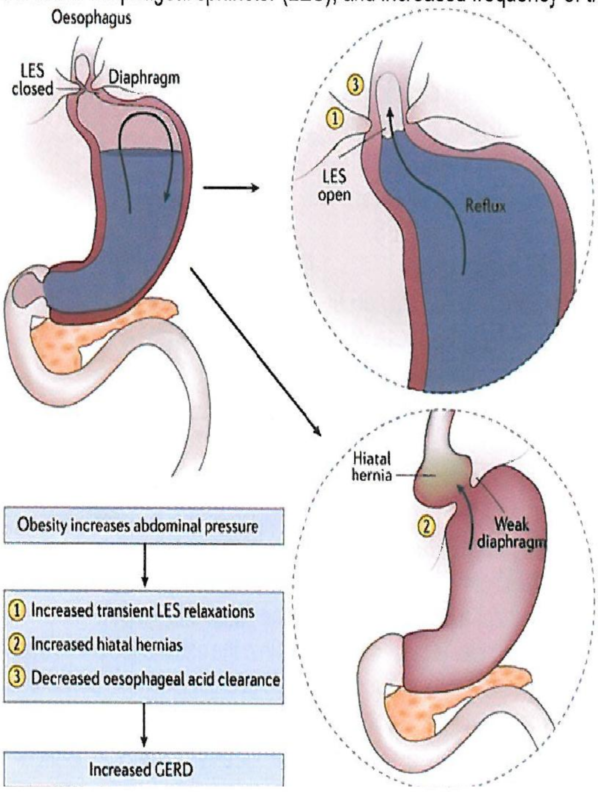
C) **Alarm symptoms** (***may be indicative of complications***): **dysphagia** (difficulty swallowing), **odynophagia** (painful swallowing), **bleeding**, *unexplained* **weight loss**, **chest pain**, **choking** (blocking air flow into the lungs) & **epigastric mass**.

D) **Complications**;

- **Esophagitis**; Ulcers in esophageal epithelium.
- **Esophageal strictures**; Persistent narrowing of the esophagus.
- **Barrett's esophagus** (*intestinal metaplasia*); Changes of the epithelial cells from squamous to intestinal columnar epithelium of the distal esophagus (precursor for esophageal cancer).
- **Esophageal adenocarcinoma**; a form of cancer.

➢ Pathophysiology:-

- **Impaired Esophageal Clearance**;
  - Esophageal clearance is an important protective mechanism against GERD.
  - This process involves peristalsis as well as the swallowing of salivary bicarbonate.
  - Abnormal peristalsis can cause inefficient and delayed acid clearance.
- **Dysfunction** of **Lower Esophageal Sphincter (LES)**;
  - LES must have a normal length and pressure and a normal number of episodes of transient relaxation.
  - LES dysfunction occurs via one of several mechanisms: transient relaxation of the LES (most common mechanism), permanent LES relaxation, and transient increase of intra-abdominal pressure that overcomes the LES pressure.
- **Delayed Gastric Emptying**;
  - Delayed gastric emptying increase intra-gastric pressure and increased pressure against the lower esophageal sphincter (LES).
  - This pressure eventually defeats the LES and leads to reflux.
- **Hiatal Hernia** (Bulging of top of stomach up into the diaphragm);
  - Reflux is facilitated by the presence of a hiatus hernia.
  - The LES pressure is decreased
  - Esophageal clearance of acid is decreased in the presence of a hiatus hernia.
    → increased reflux and more severe esophagitis.
- **Obesity**;
  - High body mass index (BMI) increases esophageal acid exposure (not completely understood), but may due to;
    - Increased intragastric pressure and gastroesophageal pressure gradient, incompetence of the lower esophageal sphincter (LES), and increased frequency of transient LES relaxations.


Oesophagus
LES closed
Diaphragm
③
①
LES open
Reflux
Hiatal hernia
②
Weak diaphragm
Obesity increases abdominal pressure
① Increased transient LES relaxations
② Increased hiatal hernias
③ Decreased oesophageal acid clearance
Increased GERD

Causes:-

- A *functional* (frequent transient LES relaxation) or *mechanical* (hypotensive LES) problem of the LES is the ***most common*** cause of GERD.
  - **Transient relaxation of the LES** *can be caused by*;
    - **Foods/drinks**; **Fatty meal, Coffee, Cola, Alcohol, Chocolate, Garlic, Onion** and **Peppermint**.
    - **Medications**; **Nicotine, Nitrates, Calcium Channel Blockers, Anticholinergics, Tetracycline, Theophylline**, and **alpha** and **beta-blockers** and **Benzodiazepines**.
    - **Hormones**; **Dopamine, Estrogen** and **Progesterone**.

- **Prokinetic Agents** such as **Metoclopramide** and **Domperidone**; ***help*** **strengthen** the **lower esophageal sphincter** (**LES**) and cause the **contents of the stomach** to **empty *faster***.

Direct Irritants to the Esophageal Mucosa

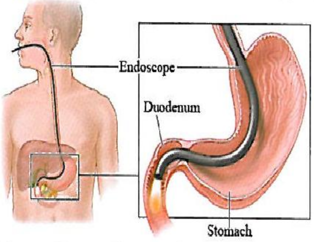
- **Foods**; **Spicy foods, Orange juice, Tomato juice** and **Coffee**.
- **Medications**; **Bisphosphonates, NSAIDs, Iron, Quinidine** and **Potassium chloride**.

Risk Factors:-

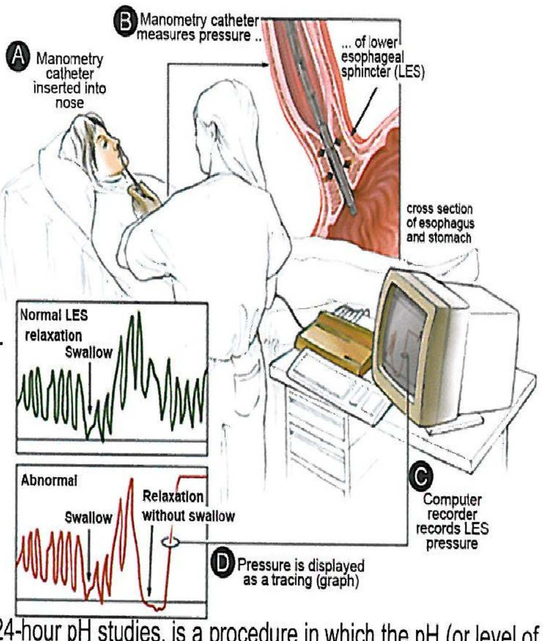
- **Obesity**, **hiatal hernia**, **food/medications affect LES**, **smoking**, **pregnancy**, **dry mouth**, **asthma**, **diabetes** and **delayed stomach emptying**.

Diagnosis:-

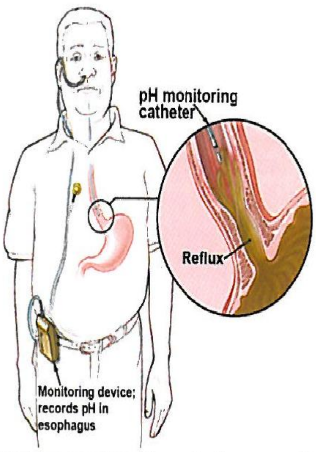
- **Patients symptoms and history**; **Typical symptoms** (**heartburn** and **regurgitation**) is *correct* in **70%** of patients.
- **Endoscopy**;
  - Upper endoscopy is not necessary in the presence of typical GERD symptoms.
  - Endoscopy is recommended in the presence of alarm symptoms and in the screening of patients at high risk of complications.
  - Repeat endoscopy is not indicated in patients without Barrett esophagus in absence of new symptoms.


Endoscope
Duodenum
Stomach

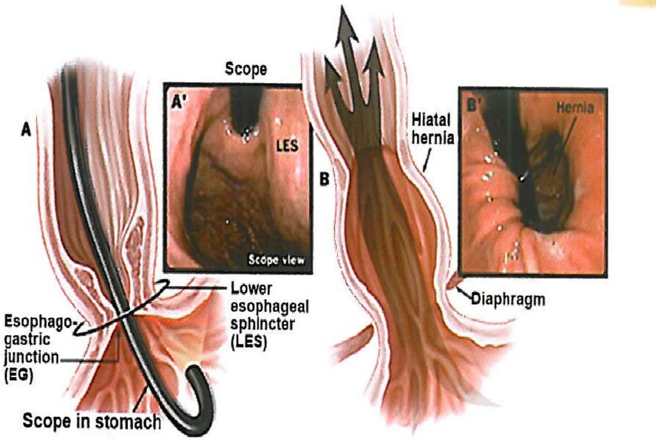
- **Esophageal Manometry**;
  - Esophageal manometry, also referred to as esophageal motility studies, involves the placement of a pressure sensitive catheter into the esophagus.
  - Test permits evaluation of the strength and coordination of muscle contractions, as well as the strength and relaxation function of the LES.
  - Although low LES pressure is suggestive of GERD, GERD may occur in patients with normal LES pressure.
  - Therefore, the results of esophageal manometry are not reliable for the diagnosis of GERD.
  - Recommended for preoperative evaluation.


B Manometry catheter measures pressure ..
... of lower esophageal sphincter (LES)
A Manometry catheter inserted into nose
cross section of esophagus and stomach
Normal LES relaxation
Swallow
Abnormal
Swallow
Relaxation without swallow
C Computer recorder records LES pressure
D Pressure is displayed as a tracing (graph)

- **Ambulatory pH monitoring**;
  - Continuous pH monitoring, also called 24-hour pH studies, is a procedure in which the pH (or level of acidity) is recorded for a prolonged period (*see photo; next page*).
  - An acid-sensitive catheter is placed from nose into the esophagus and is attached to a small monitoring device that records changes in esophageal pH over an extended period of time (up to 24 hours).
  - It provides information on the severity and pattern of reflux.
  - Useful for before considering endoscopic or surgical therapy in patients not responding to acid-suppression therapy.
- ***N.B***; Screening for H. pylori is not recommended.


pH monitoring catheter
Reflux
Monitoring device; records pH in esophagus

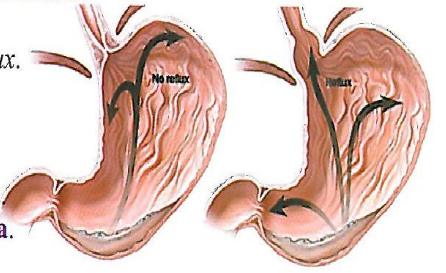
Patient set-up for pH monitoring


A
Scope
A'
LES
Scope view
Esophago-gastric junction (EG)
Lower esophageal sphincter (LES)
Scope in stomach
B
Hiatal hernia
B'
Hernia
Diaphragm

A, Normal esophagogastric (EG) junction; B, hiatus hernia; A', B', endoscopic views.

➢ Treatments:-

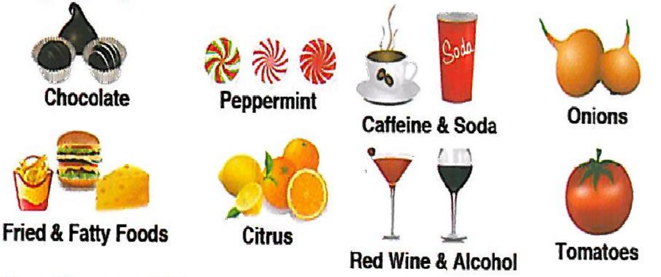
- **Goals**;
  1) *Decrease* or *prevent* **symptoms**.
  2) *Decrease* **frequency** or *recurrence* and *duration* of **gastroesophageal reflux**.
  3) *Promote* **healing** of the **injured mucosa**.
  4) *Prevent* the *development* of **complications**.
- **Therapy is directed at**;
  1) *Decreasing* the **acidity** of the *reflux*.
  2) *Decreasing* the **gastric volume**.
  3) *Improving* **gastric emptying**.
  4) *Increasing* **LES pressure**.
  5) *Enhancing* **esophageal clearance**.
  6) *Protecting* the **esophageal mucosa**.


No reflux
Reflux

- **Options**;
  1) **Lifestyle modifications**. 2) **Pharmacological therapy**. 3) **Anti-reflux surgery**.

Lifestyle Modifications

A) Dietary modifications (If symptoms are associated with certain foods or drinks);
- ***Avoid*** **foods/drinks** *may reduce* **LES pressure**;
  - Caffeine (**Coffee** and **Cola**), Alcohol, Chocolate, Garlic, Onion & Peppermint.
- ***Avoid*** **foods/drinks** *may cause* **irritants** to the **esophageal mucosa**;
  - Spicy foods, Orange juice, Tomato juice and Coffee.
- ***Reduce*** **fat intake** (*high-fat meals slow gastric emptying*).
- ***Avoid*** **eating 2–3 hours before bedtime**.
- ***Remain*** **upright** ***after*** **meals**.


Chocolate
Peppermint
Caffeine & Soda
Soda
Onions
Fried & Fatty Foods
Citrus
Red Wine & Alcohol
Tomatoes

B) Weight loss if overweight.

C) Reduce or discontinue nicotine use in tobacco products.

D) Elevate head of bed.

E) Avoid tight-fitting clothing (decreases intra-abdominal pressure).

F) Avoid medications ***that may*** **reduce LES pressure**, **delay gastric emptying**, or cause **direct irritation**: Nicotine, Nitrates, Calcium Channel Blockers, Anticholinergics, *Tetracycline*, *Theophylline*, alpha/beta-blockers, Benzodiazepines, Opiates, Tricyclic antidepressants and NSAIDs.

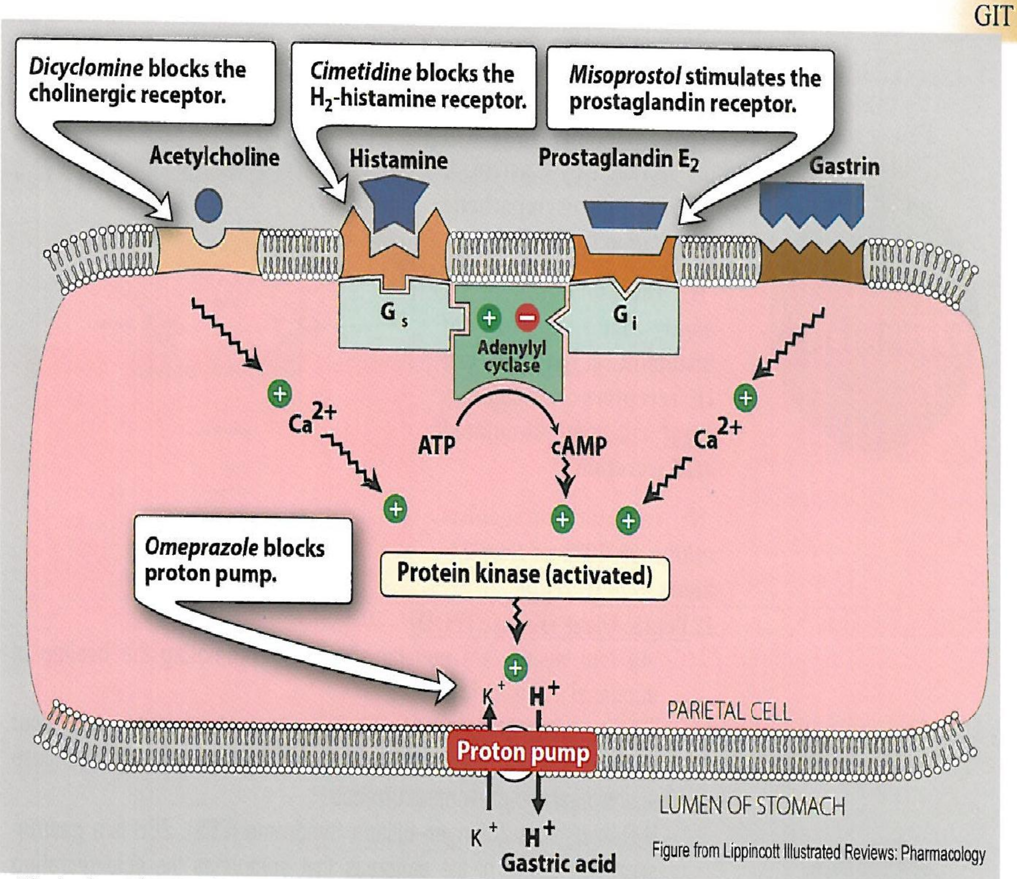
Pharmacological Therapy

- **Patients** may ***benefit from*** **lifestyle modifications** ***but*** **most** will ***require*** **pharmacological therapy** to ***control*** **symptoms**.
- ***Initial*** **treatment** ***depends on*** the **severity**, **frequency** and **duration** of **symptoms**.
  - A) ***Step-down treatment***; ***Start*** *with* **maximal dose therapy** (first-line strategy in esophageal erosion).
  - B) ***Step-up*** **treatment**; ***Start*** *with* ***lower*-dose over-the-counter (OTC) products**.
- ***Pharmacological options***;
  - A) **Antacids**.
  - B) **Acid-Suppression Therapy**; *such as* **H_2 receptor blockers** & **Proton Pump Inhibitors (PPIs)**.
  - C) **Promotility (Prokinetic) Agents**; *such as* **Cisapride**, **Metoclopramide** and **Bethanechol**.

Antacids

Aluminum Hydroxide [$Al(OH)_2$]	**Magnesium Hydroxide** [$Mg(OH)_2$]
Calcium Carbonate [$CaCO_3$]	**Sodium Bicarbonate** [$NaHCO_3$]

- **Antacids**; **Aluminum Hydroxide** [$Al(OH)_2$], **Magnesium Hydroxide** [$Mg(OH)_2$], **Calcium Carbonate** [$CaCO_3$] and **Sodium Bicarbonate** [$NaHCO_3$] are ***weak bases*** that *react with* **gastric acid** to form **water** and a **salt** to ***diminish*** **gastric acidity**.
- **Calcium Carbonate** are also used as ***calcium supplements*** for the *treatment of* **osteoporosis**.
- **Antacids** also ***reduce*** **pepsin** (proteolytic enzyme) ***activity***, *because* **pepsin** is ***inactive*** at a **pH** ***greater than*** 4.
- ***Formulations***; **Antacid products** are *available* **OTC** in a wide variety of formulations (**capsules, tablets, chewable tablets** and **suspensions**).
- Maalox® and Mucogel®; **Aluminum Hydroxide** + **Magnesium Hydroxide**.
- **Antacids** *may be* ***formulated with*** *other* **active ingredients** like **Simethicone** (Maalox® plus) or **Dimethicone** (Epicogel®) to ***control gas*** or **Alginic Acid** (Gaviscon®) act as a ***physical barrier***.
- Gaviscon® contain the ***anti-refluxant*** **Alginic Acid**, which forms a ***viscous layer*** on ***top of*** **gastric contents** to act as a ***barrier*** to **reflux** (*variable added efficacy*).
- ***Mechanism of action***; **Neutralizing** **gastric acid** → ***decrease*** of **pepsin** → ***increase*** **LES pressure**.
- ***Advantages***; ***Rapid*** **onset of action**.
- ***Disadvantages***; ***Short*** **duration of action** (*need frequent dosing*).
- ***Therapeutic uses***; ***Symptomatic relief*** of **peptic ulcer disease** and **GERD**.
  - ***First-line therapy*** for **mild** or ***infrequent*** [or ***intermittent***] (*less than twice weekly*) **symptoms**.
  - ***Not appropriate*** for **healing** *established* **esophageal erosions**.
- ***Side effects***; **Constipation** (**Aluminum**; *hALts stool*), **diarrhea** (**Magnesium**; *magnifies stool*), ***accumulation*** of **Aluminum** and **Magnesium** in **renal disease** (with repeated dosing).
- ***Because*** of their ***systemic effects***, **Calcium** and **Bicarbonate** ***salts*** are ***less popular*** as **antacids**.
- ***Drug interactions***;
  - ***Chelation***; *reduce absorption of*; **Fluoroquinolones** and **Tetracyclines**.
  - ***Increases*** **pH**; *reduce absorption of*; **Ketoconazole**, **Itraconazole**, **Iron**, **Atazanavir**, **Delavirdine**, **Indinavir** and **Nelfinavir**.
  - ***Increases*** **pH**; *reduce absorption of*; **Raltegravir** and **Saquinavir** (*leading to potential toxicity*).



Dicyclomine blocks the cholinergic receptor.

Cimetidine blocks the H_2-histamine receptor.

Misoprostol stimulates the prostaglandin receptor.

Omeprazole blocks proton pump.

Figure from Lippincott Illustrated Reviews: Pharmacology

- Effects of acetylcholine, histamine, prostaglandin E_2, and gastrin on gastric acid secretion by the parietal cells of stomach.
- Gs; Stimulatory G-protein coupling to adenylyl cyclase. - Gi; inhibitory G-protein coupling to adenylyl cyclase.

Acid-Suppression Therapy

H_2-receptor Antagonists (H_2RAs)

- The **H_2 receptor antagonists (H_2RAs)** are ***reversibly inhibit*** **histamine-2 receptors**, ***block*** the ***stimulatory effect*** of **Histamine** on **gastric parietal cell**, ***decreasing*** the **production of gastric acid**.

Cimetidine (Tagamet®)	**Ranitidine** (Zantac®)
Nizatidine (Ulcfree®)	**Famotidine** (Antodine®)

- **Cimetidine** [sye-ME-ti-deen], **Ranitidine** [ra-NI-ti-deen], **Famotidine** [fa-MOE-tideen], and **Nizatidine** [nye-ZA-ti-deen] are ***reduces*** the **secretion of gastric acid** by ***blocking*** **H_2 receptors.**
- **Cimetidine** is ***largely replaced*** by ***other*** **H_2 receptor blocker** *due to* **side effects.**

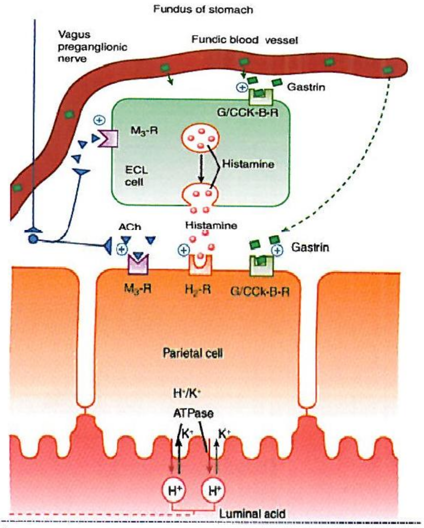
Pharmaco Kinetics

- ***All*** **four agents** are *rapidly* **absorbed** from the intestine.
- **Cimetidine**, **Ranitidine** and **Famotidine** ⇨ ***first-pass hepatic metabolism*** (**bioavailability** = approximately 50%), **Nizatidine** has ***little*** **first-pass hepatic metabolism.**
- ***Half-life*** of four agents approximately 1.1 to 4 hours.
- ***Duration of action*** depend on the dose given.
- ***Dose reduction*** is **required** in ***moderate*** to ***severe*** **renal dysfunction** and ***severe*** **hepatic impairment.**

Drug	Relative potency	Usual dose	Parenteral form
Cimetidine	1	400 mg twice or 800 mg at bedtime	50 mg
Ranitidine	4-10	150 mg twice or 300 mg at bedtime	50 mg
Nizatidine	4-10	150 mg twice or 300 mg at bedtime	Not available
Famotidine	20-50	20 mg twice or 40 mg at bedtime	20 mg

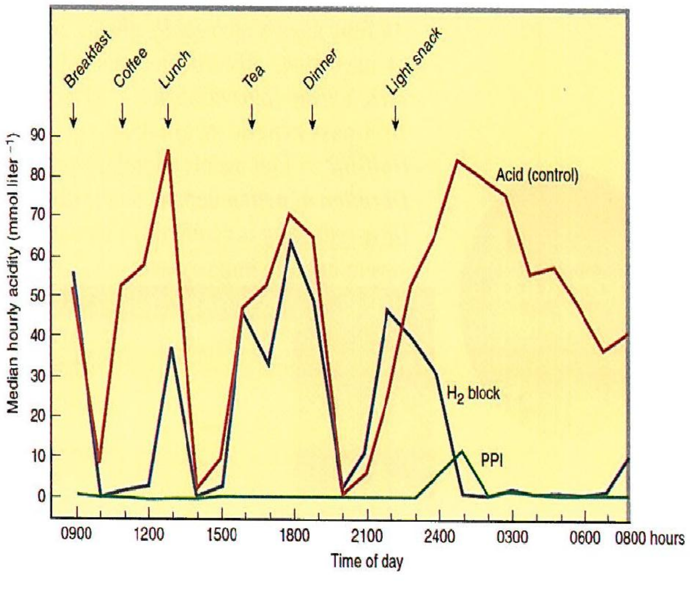
Mechanism OF Action

- **Histamine** ***released from*** **enterochromaffin-like (ECL) cells** in the ***fundus*** of the **stomach** by **Gastrin** or ***vagal*** **parasympathetic** ***stimulation*** (**Acetylcholine**)
- **H_2 receptor antagonists** ***block*** the ***actions*** of **histamine** at **parietal cell H_2 receptors** and ***suppress*** ***basal*** and ***meal*** **stimulated acid secretion.**
- **H_2 receptor antagonists** ***inhibit*** **60-70%** of ***total*** **24-hours** ***acid secretion.***



Therapeutic Uses

1) **Peptic Ulcer Disease (PUD):**
   - ***All four agents*** are ***equally*** effective in **promoting** the **healing** of **duodenal** and **gastric ulcers.**
   - **PPIs** have ***largely replaced*** **H_2RAs** in the treatment of ***acute*** **peptic ulcer (NSAID-induced ulcers** and **ulcer caused by *H.pylori*),** ***because*** these agents ***heal*** and ***prevent*** **recurrence.**
   - **H_2RAs** ***used*** in **Zollinger–Ellison Syndrome (ZES),** ZES is a ***gastrin-secreting tumor*** of the **pancreas** that ***stimulates*** the **acid-secreting cells** of the **stomach,** cause **mucosal ulceration.**
2) **Gastroesophageal Reflux Disease (GERD):**
   - ***Therapy with*** **H_2RAs** is ***less efficacious than*** therapy with **PPIs** in ***healing*** **erosive esophagitis.**
   - **H_2RAs** act by ***stopping*** **acid secretion.** Therefore, they may ***not relieve*** **symptoms** for at **least 45 minutes.**
   - **Antacids** more quickly and efficiently **neutralize** stomach acid, but their action is only ***temporary.***
3) **Non-ulcer Dyspepsia:**
   - ***Commonly used*** for **dyspepsia** ***not caused*** by **peptic ulcer.**
4) **Acute Stress Ulcers:**
   - **H_2RAs** given as an **IV infusion** to prevent and manage acute stress ulcers.
   - **PPIs** are ***favor*** for this indication.



Red; Twenty-four-hour median intragastric acidity pre-treatment.

Blue; After 1 month of treatment with ranitidine, 150 mg twice daily.

Green; After 1 month of treatment with omeprazole 20 mg once daily (PPI).

- ***Notes;***
  - **H_2-receptor antagonists** have a ***marked effect*** on **nocturnal acid secretion** but only a ***modest*** **effect** on **meal-stimulated secretion.**
  - **Proton pump inhibitors (PPIs)** ***markedly suppress*** **meal-stimulated** and **nocturnal acid secretion.**

Side Effects

- **H₂-antagonists** are extremely **safe drugs**.
- *Side effects* occur in > 3% of patient; **diarrhea, headache & fatigue**.
- **Cimetidine** ***inhibits*** binding of **Dihydrotestosterone** to **androgen receptors** (*Anti-androgenic effect*) and ***increase*** **serum prolactin**, ***long term use*** may *cause*:
    - **Impotence** in *male* (Anti-androgenic effect).
    - **Gynecomastia** in *male* (Increase prolactin).
    - **Galactorrhea** and **amenorrhea** in *female* (Increase prolactin).
- ***Rapid*** IV **infusion** of **H₂-antagonists** may *rarely* cause **bradycardia** and **hypotension** by blocking cardiac H₂-receptors.

- ***Pregnancy*** ⇨ **FDA category B.**

Drug Interactions

- **Cimetidine** ***inhibits several*** **cytochrome P450** *isoenzymes* (***LME inhibitor***) and can *interfere with* the ***metabolism*** of many **other drugs**, such as **Warfarin** and **Phenytoin**.
- ***All of*** **H₂-antagonists** ***except*** **Famotidine** ***inhibit*** **gastric** *first pass metabolism* of **Ethanol** *especially* in **women** *resulting in* ***increased bioavailability*** of **Ethanol** ⇨ ***increase*** **blood Ethanol** ***level***.
- **H₂-antagonists** ***compete*** with **Creatinine** and **certain drugs** (e.g. **Procainamide**) for **renal tubular** ***secretion***.

Proton Pump Inhibitors (PPIs)

Omeprazole (Pepzol®) (Prilosec®)	**Esomeprazole** (Nexium®)
Lansoprazole (Lanzor®) (Prevacid®)	**Dexlansoprazole** (Dexilant®)
Pantoprazole (Controloc®)	**Rabeprazole** (Pariet®)

- ***Six*** **proton pump inhibitors (PPIs)** are *available for* **clinical use**; **Omeprazole** [oh-MEH-pra-zole], **Esomeprazole** [es-oh-MEH-pra-zole], **Lansoprazole** [lan-SO-pra-zole], **Dexlansoprazole** [DEX-lan-SO-pra-zole], **Pantoprazole** [pan-TOE-pra-zole] and **Rabeprazole** [rah-BEH-pra-zole].
- **Omeprazole** and **Lansoprazole** are ***racemic mixtures*** (*R & S*).
  * **Esomeprazole** is the *S-isomer* of **Omeprazole**. * **Dexlansoprazole** the *R-isomer* of **Lansoprazole**.

Pharmaco Kinetics

- ***All*** **PPIs** are *effective* ***orally***.
- **Esomeprazole**, **Lansoprazole**, and **Pantoprazole** are also ***available*** in **IV formulations**.
- **Omeprazole** is also *available for* **IV injection** in Europe.
- ***All*** **PPIs** are ***prodrugs***.
- ***All oral*** **PPIs** are ***formulated as*** **acid-resistant enteric coated** to ***protect*** them from ***premature*** **degradation** by **gastric acid**.
- The **coating** is ***removed*** in the **alkaline** ***duodenum***, and the ***prodrug***, a **weak base**, is ***absorbed*** and ***transported*** to the **parietal cell**.
    - ***N.B***; For children or patients with dysphagia or enteral feeding tubes, **capsule formulations** (*but* ***not tablets***) may be opened and the **microgranules** mixed with apple or orange juice or mixed with soft foods.
- **Omeprazole**, **Lansoprazole** and **Esomeprazole** is *also available as* a ***gastro-resistant granules*** as a ***powder for*** **oral suspension** or **tablet formulation** that ***disintegrates*** in the **mouth**, or it may *mixed with* **water**.
- **Omeprazole** is also available as a ***powder formulation*** (**capsule** or **packet**) that contains **Sodium Bicarbonate** (Zegerid®) to ***raise*** **gastric pH** to ***protect*** **Omeprazole** *from* **acid** ***degradation***.
- **Dexlansoprazole** has a ***delayed release formulation***.
- ***All*** **PPIs** ***should be*** ***administered*** *approximately* **30-60 minutes** ***before*** a **meal** (usually breakfast); ***bioavailability*** of all agents is decreased *approximately* **50%** by ***food***.
- ***Serum*** **half-life**; **1.5 hours**, ***but*** **acid inhibition** ***lasts up*** to **24 hours** (irreversible inactivation of the proton pump).
- ***Full acid inhibiting*** are *occur* ***after 3–4 days*** of ***daily dose***, similarly, ***after stopping*** the drug, it takes **3–4 days** for ***full acid secretion*** to *return*.

Pharmaco Kinetics

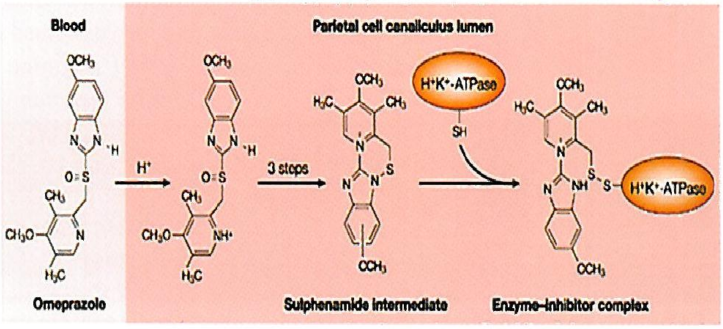
Drug	Relative potency	Usual dose	Parenteral form
Omeprazole	1	20-40 mg once/d	
Esomeprazole	1.6	20-40 mg once/d	IV 20, 40-mg/vial
Lansoprazole	0.9	15-30 mg once/d	IV 30 mg/vial
Dexlansoprazole	data not available	30-60 mg once/d	
Pantoprazole	0.23	20-40 mg once/d	IV 40 mg/vial
Rabeprazole	1.82	10-20 mg once/d	

- ***Metabolism***; ***All* PPIs** are ***metabolized by*** **hepatic P450 cytochromes**, including **CYP2C19** and **CYP3A4**.
- *Excretion*; **Metabolites** are *excreted* in **urine** and **feces**.

- In ***contrast*** to **H_2 antagonists**, **proton pump inhibitors *inhibit*** *both* **fasting** and **meal-stimulated secretion** *because* they ***block*** the ***final*** *common* **pathway** of **acid secretion**.
- In ***standard doses***, **proton pump inhibitors *inhibit* 90–98%** of **24-hour acid secretion**.

Mechanism OF Action

- **Active drugs** of **proton pump inhibitors *blocks* proton pump** by ***forms*** a ***stable* covalent bond** (***irreversible***) with the **H^+/K^+-ATPase enzyme**.



- At least **18 hours** are *required for* ***resynthesized*** of ***new*** **H^+/K^+-ATPase enzyme**, and **acid *secretion*** is ***inhibited*** *during this* **time**.

Therapeutic Uses

1) **Gastroesophageal Reflux Disease (GERD)**;
   - ***All* PPIs** are *the* ***most effective agents*** "**gold-standard**" for the *treatment of*;
     - **Non-erosive** and **erosive reflux disease**.
     - **GERD esophageal complications** (**peptic stricture** or **Barrett's esophagus**).
     - **Extraesophageal complications** (***asthma***, ***chronic cough***, ***laryngitis*** and ***non-cardiac chest pain***).
   - ***All* PPIs *resolve*** of **GERD symptoms** *within* **4-8 weeks**.
   - ***Once*-daily PPIs** or ***twice* daily** or ***adding*** an **H_2 antagonist** are an ***options*** for treatment *according to* **severity**.
   - **GERD symptoms *recur*** in *over* **80%** of **patients** *within* **6 months *after*** **discontinuation** of a **PPIs**.
2) **Peptic Ulcer Disease (PUD)**;
   - **PPIs**; ***more rapid*** **symptom relief** and ***faster*** **ulcer healing** for **duodenal ulcers** *than* **H_2 antagonists**.
   - ***All* PPIs heal *more than* 90%** of **duodenal ulcers** *within* **4 weeks** and **gastric ulcers** *within* **6–8 weeks**.
     - ***H. pylori*-associated ulcers**.
     - **NSAID-associated ulcers**.
     - **Prevention of re-bleeding from peptic ulcers**.
     - **Zollinger–Ellison Syndrome (ZES)**.
3) **Non-ulcer Dyspepsia**;
   - **PPIs** have ***modest*** **efficacy** for non-ulcer dyspepsia (benefiting 10–20%).
4) **Acute Stress Ulcers**;
   - ***Oral* Omeprazole *formulation***, which is *administered by* **nasogastric tube twice daily** on the ***first day***, then **once daily**.

Side Effects

- *In general*; **PPIs** are ***extremely safe***, **diarrhea**, **headache**, and **abdominal pain** are reported only in **1–5%** of **patients**.
- **Respiratory** and **Enteric Infections**;
  - **Gastric acid** is an ***important barrier*** to **colonization** and ***infection*** of the **stomach** and **intestine** from *ingested bacteria*.
    - ***Clostridium difficile*** **infection**.
    - **Upper respiratory tract infection** (***pneumonia***).
- *Long-term side effects*;
  - **Gastric acid** is ***important for*** **absorption** of; **Vitamin B12**, **Iron**, **Calcium** and **Magnesium**.
    - *Long term use of* **PPIs**; ***risk for*** **osteoporosis** (**Calcium Citrate** is the ***preferred*** **calcium supplement** in ***patients taking*** **PPIs** and ***ensure adequate*** **Vitamin D**), ***severe*** **life-threatening hypomagnesemia** with *secondary* **hypocalcemia**.
    - *Effects of* **Vitamin B12** and **Iron** ***malabsorption*** is ***clinically*** **insignificant**.
  - ***Long term use of*** **PPIs** (*especially* **Omeprazole**) have also been *associated with* ***several cases*** of **acute interstitial nephritis**.

- *Pregnancy* ⇨ ***All*** **PPIs** are **FDA category B**, *except* **Omeprazole**, is **category C**.

Drug Interactions

1) **Drugs** *with* **pH-dependent** ***absorption***; **Ketoconazole**, **Itraconazole**, **Protease inhibitors** (antiviral drugs).

- ***All*** **PPIs** are ***metabolized by*** **CYP2C19** and **CYP3A4**, ***because*** of the ***short half-lives*** of (*about 1.5 hours*) **PPIs**, ***clinically*** **significant drug interactions** are ***rare***.

2) **Inhibition of CYP450**;
   - **Omeprazole** ***may inhibit*** the **metabolism of Warfarin**, **Diazepam** and **Phenytoin**.
   - **Esomeprazole** ***may decrease*** **metabolism** of **Diazepam**.
   - **Lansoprazole** ***may enhance*** **clearance** of **Theophylline**.
   - **Rabeprazole** & **Pantoprazole** have ***no significant drug interactions***.
3) **Inhibition of CYP2C19**;
   - **Clopidogrel** (***antiplatelet***) is a **prodrug** that ***requires*** **CYP2C19**.
   - ***In 2009***, the **FDA** issued a public-health ***warning*** about the ***possible interaction*** between **Clopidogrel** and **Omeprazole**.
   - ***The 2013*** **American College of Gastroenterology (AGA) guidelines** consider the **PPI/clopidogrel** ***interaction NOT clinically significant***.
   - ***Recent*** (***2015***) **meta-analysis study**; In summary, suggest that the highly controversial ***interaction between*** **PPIs** (**Omeprazole**) and **Clopidogrel** observed in platelet aggregation studies has ***no clinical significance***.
4) ***high-dose*** **IV Methotrexate**;
   - ***Higher risk*** of **methotrexate toxicity**.
   - **Patients receiving** ***high-dose IV*** **Methotrexate** should ***avoid*** **PPI** use, with a switch to **Ranitidine** if needed, for **2 days** ***before*** and ***after*** **Methotrexate** administration *may prevent* the ***interaction***.

Promotility (Prokinetic) Agents

- ***Promotility** (**Prokinetic**) **agents*** are a type of drug which ***enhance*** **gastric emptying** and ***enhance*** **intestinal contractions.**
- They are **used** to *relieve* **GI symptoms** such as **abdominal discomfort, bloating, constipation, heart burn, nausea** and **vomiting.**
- **Prokinetic in GERD**;
  - ***Generally***; ***Prokinetic agents*** are ***not effective as*** **acid suppression therapy.**
  - **Prokinetic agents** are somewhat *effective* but ***only*** in ***patients with*** **mild symptoms.**

Metoclopramide (Primperan®)

- **Metoclopramide** [MET-oh-KLOE-pra-mide] is a ***peripherally*** and ***centrally dopamine antagonist.***
- **Metoclopramide** ***increases*** **LES pressure** and ***accelerates*** **gastric emptying** (***does not improve*** **esophageal clearance**).
- ***Antiemetic properties***; **Metoclopramide** ***block*** **stimulation** of the medullary **chemoreceptor trigger zone** (CTZ) by **Dopamine** or **Dopamine-like agents** (**L-dopa** or **Apomorphine**).
- It is ***used*** to;
  - ***Treat*** **nausea** and **vomiting.**
  - **Delayed stomach emptying** in ***diabetes*** or ***following surgery*** and in **GERD.**
  - ***Also used*** to ***treat*** **migraine headaches.**
- ***Dose in*** **GERD**; **10-15 mg orally** ***up to*** **4 times a day 30 minutes** ***before*** **meals** and **at bedtime,** (depending upon symptoms being treated and clinical response).
- ***Pregnancy***; **US FDA category B.**
- ***Side effects***; **Dizziness, fatigue, somnolence, drowsiness, extrapyramidal symptoms (EPS)** and **hyperprolactinemia.**
- ***FDA warning***; **Metoclopramide** can ***cause*** **tardive dyskinesia** (***Treatment with*** **Metoclopramide** for ***longer than*** **12 weeks** ***should be*** **avoided**).

Cisapride (Propulsid®)

- **Cisapride** [SIS-a-pride] is a ***gastroprokinetic agent***, it acts ***as*** a ***Serotonin 5-HT4 receptor agonist.***
- ***Stimulation*** of the **serotonin** ***increases*** **Acetylcholine** ***release*** in the **enteric nervous system.**
- **Cisapride** ***improve*** **esophageal clearance.**
- **Cisapride** is ***no longer available*** for routine use because of ***life-threatening*** **cardiac arrhythmias,** when used in ***combination*** with drugs ***inhibiting*** **CYP3A4.**
- ***Available only*** on in **patients** whose ***other therapies*** have **failed.**

Bethanechol (Urotone®)

- **Bethanechol** [be-THAN-e-kole], is a ***parasympathomimetic choline carbamate*** that ***selectively stimulates*** **muscarinic receptors** *without any* effect on **nicotinic receptors.**
- **Bethanechol** has ***limited value*** in the ***treatment of*** **GERD** because of *unwanted* ***side effects,*** is ***not*** *routinely* ***recommended*** for **GERD.**
- It is ***used*** in **postoperative non-obstructive GIT** and **urinary tension.**
- ***Side effects***; **Diarrhea, blurred vision, abdominal cramping** and *may also* ***increase*** **gastric acid production.**
  - **Other Prokinetic drugs**; ***under investigation in used in GERD***; **Domperidone** (*peripherally dopamine antagonist*), **Itopride** (*dopamine D_2 receptor antagonist and acetylcholinesterase inhibitor*) and **Baclofen** (*$GABA_B$ receptor agonist*).

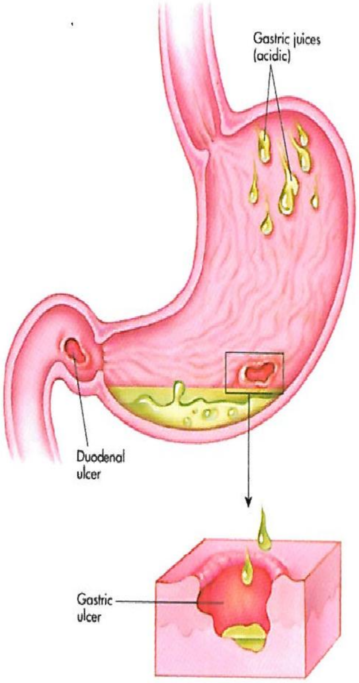
Surgical Therapy

- The ***standard*** **surgical treatment** for ***severe*** **GERD** is the **Nissen Fundoplication.**
- ***In 2012*** **FDA** ***approved*** **LINX® Reflux Management System Device** to ***augment*** **LES.**
- **Surgical therapy** is as **effective** ***as*** **medical therapy** for ***selected*** **patients** with **chronic GERD.**
- **Obese patients** *contemplating* **surgical therapy** for **GERD** should be *considered for* **bariatric surgery** (Gastric bypass is the preferred operation).

Topic Recommendations; 2013 American College of Gastroenterology (ACG) Guidelines for the Diagnosis and Management of GERD.

Peptic Ulcer Disease (PUD)

➢ Overview:-



- **Peptic Ulcer Disease** (**PUD**) ***or*** **Peptic Ulcer**, is a ***break in** the **lining of***;
  - * **Stomach** (**gastric ulcer**), ***or***
  - * *First part of* **small intestine** (**duodenal ulcer**), ***or***
  - * *Lower* **esophagus**.
- **PUD** ***differs from*** **gastritis** and **erosions** in that **ulcers** *typically **extend*** **deeper** *into the* **muscularis mucosa**.
- **Peptic ulcers** are present in ***around*** **4%** of the **population**.
- **Gastric ulcer** and **duodenal ulcer** usually *cannot be **differentiated** based on* **history alone**.
- ***Most common* symptom** is **epigastric pain**, *classically*, ***shortly*** **after meals** *with* **gastric ulcer** and **1-3 hours after meals** *with* **duodenal ulcer**.
- ***Most common causes*** are ***Helicobacter pylori*** (***H. pylori***) **infection** and **NSAIDs**.
- ***Preferred diagnostic test*** is **upper GI endoscopy**.
- ***Most patients*** with PUD are ***treated* successfully**.

➢ Prevalence:-

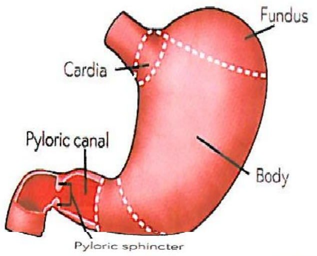
- In the **United States**, **PUD** affects *approximately* **4.5 million** people ***annually***.
- **Peptic ulcers** are present in *around* **4%** of the **population**.
- *About* **10%** of **people** *develop* a **peptic ulcer** at ***some point*** in their **life**.

➢ Classification:-

	Gastric Ulcer	Duodenal Ulcer
Common Causes	- *H. pylori* infection (70%). - NSAIDs.	- *H. pylori* infection (95%). - NSAIDs. - Low-dose aspirin.
Uncommon Causes	- Crohn's disease (CD). - Infections (cytomegalovirus, herpes simplex).	- Zollinger-Ellison syndrome (ZES). - Hypercalcemia. - Granulomatous diseases. - Neoplasia. - Infections (cytomegalovirus, herpes simplex, tuberculosis). - Ectopic pancreatic tissue.
Common Symptoms	- Epigastric pain (shortly after meals).	- Epigastric pain (1-3 hours after meals).
Associated Symptoms	- Heartburn, belching, a bloated feeling, nausea and anorexia.	

- **Esophagus Ulcer**; *results from **chronic*** **gastroesophageal reflux disease** (**GERD**), *see previous topic.*

➢ Complications:-

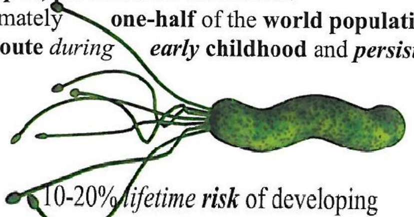


- **GI bleeding** (*most common* and can be *life-threatening*).
- **Gastric outlet obstruction** (narrowing of pyloric canal).
- **Perforation** (hole in the wall of the GIT).
  - **Penetration** is a *form of* **perforation** in which the **hole** *leads to* and the **ulcer *continues*** into ***adjacent organs*** such as the **liver** and **pancreas**.

➢ Causes:-

1) ***Helicobacter pylori*** **(*H. pylori*) infection**;

- ***H. pylori*** is a ***gram-negative***, ***helical***, ***rod-shaped***, **p*H-sensitive*** **bacterium**.
- It is ***colonizes*** the **gastric mucosa** of approximately **one-half** of the **world population**.
- It is typically ***transmitted*** *via* the **fecal-oral route** *during* ***early*** **childhood** and ***persists*** for **decades**.
- *Over* **80%** of **individuals** ***infected*** *with* the **bacterium** are ***without*** **symptoms** or **complications**.
- **Individuals** ***infected*** with ***H. pylori*** have a 10-20% *lifetime* ***risk*** of developing **peptic ulcers** (gastric and duodenal) and a **1-2%** risk of acquiring **stomach cancer**.



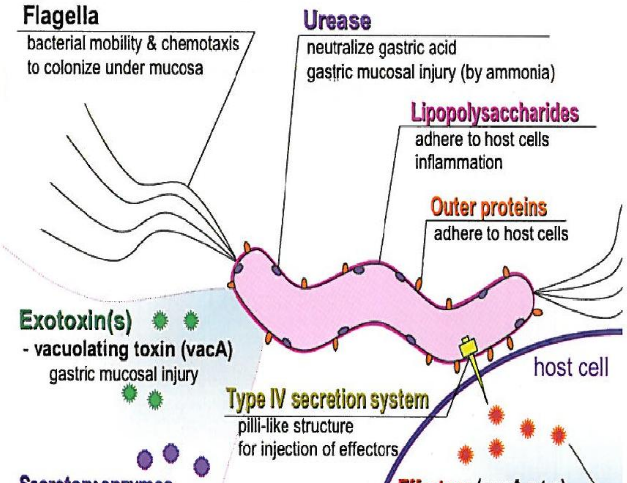
- *Pathophysiology*;
  - *H. pylori* is a pH-sensitive bacterium, uses its flagella to move towards the less acidic region and burrow into the mucus lining of the stomach to reach the epithelial cells (less acidic).
  - *H. pylori* also produces acid inhibitory proteins, which allows it to adapt to the low-pH environment of the stomach.
  - *H. pylori* harms the stomach and duodenal linings by several mechanisms, such as;

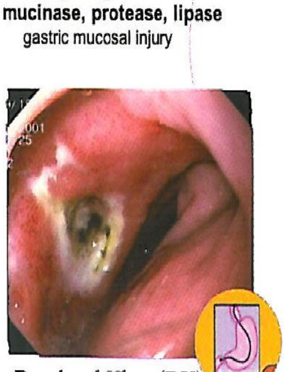
A) ***Ammonia*** (NH_3);

- *H. pylori* also neutralizes the acid in its environment by producing large amounts of urease, which breaks down the urea present in the stomach to carbon dioxide and ammonia.
- The ammonia, which is basic, then neutralizes stomach acid and is toxic to epithelial cells.

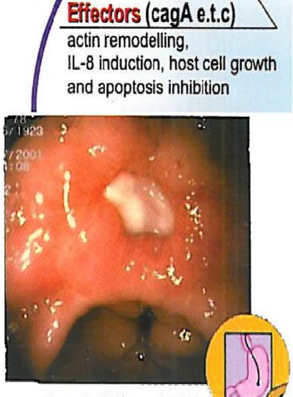
B) ***Cytotoxins***;

- *H. pylori* release Helicobacter cysteine-rich proteins (Hcp), are known to trigger an immune response, causing inflammation.
- Biochemicals and inflammatory mediators produced by H. pylori such as; proteases, vacuolating cytotoxin A (VacA) and cytotoxin associated gene CagA.
- The inflammatory response can result in atrophy of the stomach lining and eventually ulcers in the stomach. This also may increase the risk of stomach cancer.


Flagella
bacterial mobility & chemotaxis to colonize under mucosa
Urease
neutralize gastric acid
gastric mucosal injury (by ammonia)
Lipopolysaccharides
adhere to host cells
inflammation
Outer proteins
adhere to host cells
Exotoxin(s)
- vacuolating toxin (vacA)
gastric mucosal injury
Type IV secretion system
pilli-like structure
for injection of effectors
host cell
Secretory enzymes
- mucinase, protease, lipase
gastric mucosal injury
Effectors (cagA e.t.c)
actin remodelling,
IL-8 induction, host cell growth
and apoptosis inhibition



Duodenal Ulcer (DU)



Gastric Ulcer (GU)

2) Non-steroidal Anti-inflammatory Drugs (NSAIDs);

- *About* **30%** of **adults** *taking* **NSAIDs** have **GI adverse effects.**
- *Normally*; **prostaglandins** ***inhibits*** **gastric acid** ***secretion*** (PGI_2), and ***stimulate*** **synthesis of protective mucus in stomach** and **small intestine** (PGE_2 and $PGF_{2\alpha}$).
- **NSAIDs** ***inhibit*** **COX-1** ⇨ ***reduce*** **beneficial** ***effects*** of **PGs** in the **GIT**, *resulting in* ***increased*** **gastric acid secretion**, ***decrease*** **mucus protection** and ***increased*** **risk** for **GI bleeding** and **ulceration.**
- **NSAIDs** are ***weak*** **organic acids**, cause ***superficial*** **mucosal damage** *within* **minutes** of **ingestion**, and *progress to* **erosions** with ***continued use.***
- **Risk factors** for **NSAID-induced GI ulcer** and **complications**;
  - History of previous peptic ulcer disease.
  - Advanced age (>65 years).
  - Concomitant use of corticosteroids, anticoagulants or antiplatelet drugs.
  - High-dose NSAID therapy.
- **Relative risk for GI complications of some commonly used NSAIDs**;
  - **Low-risk drugs**; **Ibuprofen**, **Aceclofenac**, **Diclofenac**, **Nabumetone** and **Celecoxib.**
  - **Moderate-risk drugs**; **Naproxen** and **Meloxicam.**
  - **High-risk drugs**; **Piroxicam**, **Indomethacin**, **Ketoprofen** and **Ketorolac.**

3) Severe Physiologic Stress (Stress Ulcer);

- **Stress** *due to* **serious health problems** *such as*; **burns**, **CNS trauma**, **surgery**, and **severe medical illness** (such as; sepsis, hypotension and respiratory failure) this ***increase*** the **risk** *for* ***secondary*** (stress) **ulceration.**
- ***Severe*** **illness** and a ***decreased*** **gastric pH** are related to an ***increased*** **risk** *of* **gastric ulceration** and **hemorrhage.**

4) Lifestyle Factors;

- **Smoking** (*evidence is not conclusive*);
  - Cigarette smoking may accelerate gastric emptying and decrease pancreatic bicarbonate production.
  - Cigarette smoking impairs ulcer healing, promotes ulcer recurrence, and increases ulcer risk.
  - Smoking in the setting of *H. pylori* infection may increase the risk of relapse of PUD.
- **Caffeine**; little evidence suggests that caffeine intake is associated with an increased risk of duodenal ulcers.

5) Hypersecretory States (*rare*);

- **Zollinger–Ellison Syndrome**; **ZES** (*Gastrinomas*), ***rare*** **gastrin-secreting tumors**, also cause ***multiple*** and ***difficult-to-heal*** **ulcers.**

6) Other;

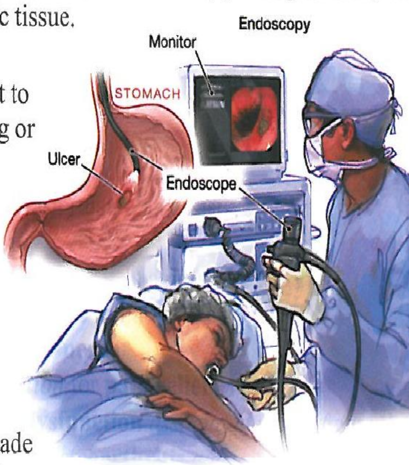
- **Genetics**; More than 20% of patients have a family history of duodenal ulcers, compared with only 5-10% in the control groups.
- Hypercalcemia, granulomatous diseases, neoplasia, infections (cytomegalovirus, herpes simplex, tuberculosis) and ectopic pancreatic tissue.

➢ Diagnosis:-

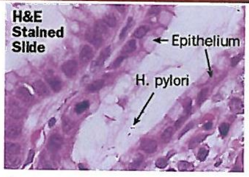
- The **history** and **physical examination** are important to identify patients at risk of ulcer, perforation, bleeding or malignancy.

1) Test for *H. pylori* infection;

- The **American College of Gastroenterology (ACG)** ***recommends*** **testing for *H. pylori* infection** in ***patients with*** **active PUD** or **history of PUD**, **dyspepsia symptoms**, or **gastric MALT** (mucosa-associated lymphoid tissue) **lymphoma.**
- The **diagnosis** of ***H. pylori*** **infection** can be made by using **endoscopic** or **non-endoscopic** tests.



A) Endoscopic (Invasive) Tests

1) Histology	- Histological examination and staining of an endoscopy biopsy. - Original method (Gold standard). - 90-95% sensitive. - 98-99% specific. - Subject to sampling error. 
2) Rapid Urease Tests	- Also known as CLO (*Campylobacter*-like organism) test. - 80-95% sensitive and 95-100% specific. - Rapid test for diagnosis. - Samples are (biopsy specimen) collected by endoscope, and placed into a medium containing urea and an pH indicator to detect change in pH in presence of ammonia (NH_3) in a sample generated by *H. pylori* urease activity. CLOtest Kimberly-Clark Rapid Urease Test = Positive = Negative - False negatives may result from; Partly treated infection, GI bleeding, achlorhydria (low or absent HCl secretion), or use of PPIs, H_2RAs or bismuth. - Patients should discontinue antisecretory agents for at least 1 week before test is performed.
3) Culture	- Culture of biopsy. - 100% specific. - High cost, technically difficult and time-consuming.

B) Non-endoscopic (Non-invasive) Tests

1) Serologic Tests	- Detect immunoglobulin G (IgG) to *H. pylori* in the serum by enzyme-linked immunosorbent assay (ELISA). - 85% sensitive. - 79% specific. - Cannot distinguish between active infection and past exposure (because antibodies persist for long periods after eradication). - Cannot use to test for eradication after treatment. - Quick (*within 15 minutes*). - Newly available tests will detect the presence of CagA or VacA antibodies. C T H. pylori S
2) Urea Breath Test (UBT)	- Detects the exhalation of radiolabeled CO_2 after the ingestion of ^{13}C- or ^{14}C-radiolabeled urea in tasteless liquid. - *H. pylori* hydrolysis of the radiolabeled urea results in CO_2 production. - If patient is infected with *H. pylori*, the breath sample will contain radioactive CO_2. - 97% sensitive and 95% specific. - Recommended test to confirm post-treatment eradication of *H. pylori*. - Recent use of antibiotics or anti-secretory agents may result in false negatives (patients should discontinue anti-secretory agents at least 2 weeks or antibiotics at least 4 weeks before testing).
3) Stool (Faecal) Antigen Tests	- Identifies *H. pylori* antigen in stool by enzyme immunoassay using polyclonal anti-*H. pylori* antibody. - 88-92% sensitive and 87% specific. - Can be used to make a diagnosis and confirm eradication. - Recent use of bismuth, antibiotics, or PPIs may also result in false negatives (patients should discontinue anti-secretory agents or antibiotics at least 2 weeks before testing).

➢ Drugs Used in Peptic Ulcer Disease (PUD):-

1) **Antimicrobial Agents**; in ***H. pylori*–associated ulcers**; see chemotherapy chapter;
    - **Amoxicillin** (*is a β-lactam antibiotic*).
    - **Clarithromycin** (*is a macrolide antibiotic*).
    - **Tetracycline** (*is a tetracycline antibiotics*).
    - **Metronidazole** (*is an antibiotic and antiprotozoal*).
    - **Tinidazole** (*like* **metronidazole**).
2) **Antacids**; *see previous topic for full illustration*.
3) **Acid-Suppression Therapy**; *see previous topic for full illustration*.
    - **H_2-Receptor Antagonists** (H_2RAs) and **Proton Pump Inhibitors** (PPIs).
4) **Prostaglandins**; **Misoprostol**.

Misoprostol (Cytotec®) (Misotac®)

- **Misoprostol** [MYE-soe-PROST-ol] is a **PGE$_1$ analogue**, ***with*** **oxytocic properties**.
- It is **approved** for ***use*** in the ***prevention*** **of NSAID-induced gastric ulcers**;
    - **NSAIDs** *inhibits* **prostaglandin synthesis**, and a *deficiency of* **prostaglandins** within the **gastric mucosa** may lead to diminishing **bicarbonate** and **mucus** ***secretion*** and may contribute to the **mucosal damage** caused by ***these agents***.
- It ***produces*** **uterine contractions** and is ***contraindicated*** *during* **pregnancy**.
- **Off-label uses**: **labor induction**, **abortion**, **missed miscarriage** and **postpartum bleeding**;
    - **Misoprostol effects** are ***dose dependent*** and include **cervical softening** and **dilation**, **uterine contractions**.
    - ***Routes of administration***; include oral, vaginal, sublingual, buccal, or rectal.
    - In **abortions** ***mainly*** **used in combination** with **Mifepristone** (*Antiprogestin*).
- ***Dear pharmacists*** this drug is prescribed only by obstetricians and gynaecologists by a trusted prescription; So don't prescribe this drug by any way because may be used by prostitutes for abortion (illegally).

5) **Mucosal Protective Agents**; **Sucralfate** and **Bismuth Subsalicylate**.
    - *Also known as* **cytoprotective compounds**, these agents have ***several actions*** that ***enhance*** **mucosal protection**, thereby ***preventing*** **mucosal injury**, ***reducing*** **inflammation** and ***healing*** **existing ulcers**.

Sucralfate (Carafate®)

- **Sucralfate** [soo-KRAL-fate] is a ***sucrose sulfate-aluminium complex*** that ***binds*** to the **ulcer**, ***creating*** a **physical barrier** that ***protects*** **ulcer** *from* **gastric acid**, *allowing* the **ulcer** *to* **heal**.
- ***Uses***; **Duodenal ulcer** and **prevention of stress ulcers**.
- Its **use** is ***limited*** due to the ***need for*** **multiple daily dosing** and ***drug-drug*** **interactions** (interfere with the absorption of other drugs).
- ***Require*** **acidic pH** for ***activation*** (**Sucralfate** is a locally acting substance that in an acidic environment {pH < 4} reacts with HCl in the stomach to form a cross-linking, viscous, paste-like material capable of acting as an acid buffer for as long as 6 to 8 hours after a single dose), ***should not*** be *administered with* **PPIs**, **H_2RAs** or **antacids**.
- **Sucralfate** ***does not prevent*** **NSAID-induced ulcers**, and it ***does not*** *heal* **gastric ulcers**.

Bismuth Subsalicylate (Pepto-Bismol®) & Bismuth Subcitrate

- **Bismuth Subsalicylate** [BIZ-muth sub-sa-LIS-a-late] is a *derivative of* **Salicylic Acid**, **Bismuth Salicylate** ***displays*** ***anti-inflammatory*** and ***bactericidal action***, and it also acts as an **antacid** and **antidiarrheal**.
- **Bismuth Subsalicylate** is ***used as*** a **component** of **quadruple therapy** to ***heal*** **peptic ulcers**.
- ***Actions***; **Antimicrobial actions**, ***inhibits*** **pepsin activity**, ***increases*** **mucus secretion**, ***coat*** and ***protect*** the **ulcer**. **Bismuth compounds** *may cause* a **black discoloration** of **tongue** & **stool**.

Lifestyle Modifications

- **Patients** *with* **PUD** *should* ***eliminate*** or ***reduce*** **psychological stress**, **cigarette smoking**, and the **use of NSAIDs** (*including* **Aspirin**).
- There is ***no*** **anti-ulcer diet**, the **patient** ***should*** **avoid foods** and **beverages** that cause **dyspepsia** or that **exacerbate ulcer symptoms** (e.g., **spicy foods**, **caffeine**, and **alcohol**).

Pharmacologic Therapy

Treatment of *H. pylori* Associated Ulcers

Recommendations

- *General recommendations*, *based on* **American College of Gastroenterology (ACG) guidelines**;
  - * **Triple-based therapy**; are **triple-based therapy** include an **antisecretory agent** (*preferably a* PPI) ***plus*** *at least* **two antibiotics** (**Clarithromycin** and **Amoxicillin** *or* **Metronidazole**).
    - **Therapy duration**; is 7–14 **days**, *depending on* the **regimen chosen** (**14 days** is ***preferred***).
    - **Follow-up testing**; for **eradication *should be* performed** in *patients with* a history of **ulcer complication** or **recurrence of symptoms**; **Urea breath test** or **stool antigen tests** are *preferred for **confirming eradication*** (should wait at least 4 weeks after treatment for both).
  - * **Quadruple-based therapy** (**Bismuth Subsalicylate**, **Metronidazole**, **Tetracycline** and **PPI** *for* **14 days**) are **considered a *first-line treatment*** in ***patient with*** **triple-based therapy fails** or **intolerance** or **allergy** to **components** of the ***triple-drug therapy***.
  - * **Sequential therapy**; involved ***administration of*** a **PPI** and **Amoxicillin** given *first for* the **first 5 days,** *followed by* a **PPI**, **Clarithromycin**, and **Tinidazole** for an *additional* **5 days**.
  - * **Salvage therapy**; **Bismuth-based quadruple therapy** for **14 days** or **Levofloxacin-based triple therapy** for **10 days** be used in patients who have ***not responded*** to **initial regimens**.

Regimen	Duration	Efficacy (%)
First Line		
Standard Triple Therapy		
* PPI + Amoxicillin 1 g BID + Clarithromycin 500 mg BID ***OR*** * PPI + Metronidazole 500 mg BID + Clarithromycin 500 mg BID	10–14 Days	70–85
Sequential Therapy		
* PPI + Amoxicillin 1 g BID for **5 days**, then PPI, Clarithromycin 500 mg BID + Tinidazole 500 mg BID for **5 days**	10 Days (5+5)	> 90
Second Line		
Non–bismuth-based Quadruple Therapy		
* PPI + Amoxicillin 1 g BID + Clarithromycin 500 mg BID + Tinidazole 500 mg BID (*or* Metronidazole 500 mg BID)	10 Days	90
Bismuth-based Quadruple Therapy		
* Bismuth Subsalicylate 525 mg QID + Metronidazole 500 mg TID + Tetracycline 500 mg QID + PPI BID	14 Days	75–90
* {Bismuth Subcitrate 420 mg + Tetracycline 375 mg + Metronidazole 375 mg (Pylera®) QID} + PPI BID	10 Days	85–92
Levofloxacin-based Triple Therapy		
* PPI + Amoxicillin 1 g BID + Levofloxacin 500 mg once daily	10 Days	-

PPI = **Omeprazole** 20 mg BID **or** **Lansoprazole** 30 mg BID **or** **Esomeprazole** 40 mg once daily **or** **Rabeprazole** 20 mg PO BID (**Pantoprazole** or **Dexlansoprazole** *not* FDA-approved indication for *H. pylori* eradication).

BID = twice daily; PO = orally; PPI = proton pump inhibitor; QID = 4 times/day; TID = 3 times/day

- **Metronidazole** can be *substituted for* **Amoxicillin** or **Clarithromycin** in patients with **penicillin** or **macrolide** ***allergy*** for the **triple-drug regimens**, treat for **14 days** in this instance.

Primary Prevention of NSAID-Induced Ulcers

Recommendations

- ***General recommendations***, *based on* **American College of Gastroenterology** (ACG) **guidelines**;
  - * **Risk factor** ***modification***.
  - * ***Test*** and ***treat*** for *H. pylori* if patient is beginning **long-term NSAID therapy**.
  - * ***Determine*** **level** of **GI-related risk** using *this table*;

Category	Risk Factors
High risk	- History of complicated ulcer. - Several (>2) risk factors. - Concomitant use of corticosteroids, anticoagulants or antiplatelet drugs.
Moderate risk (1 or 2 risk factors)	- Age >65 years. - High-dose NSAID therapy. - History of uncomplicated ulcer. - Concurrent use of aspirin (including low dose), corticosteroids or anticoagulants.
Low risk	- No risk factors.

→ If ***low* CV risk** and:

- ***Low* GI risk** → **NSAID** (*lowest dose*).
- ***Moderate* GI risk** → **NSAID + PPI *or* Misoprostol** (800 mcg/day in divided doses).
- ***High* GI risk** → **COX-2 inhibitor + PPI *or* Misoprostol** (800 mcg/day in divided doses).

→ If ***high* CV risk** (***requirement for*** *low-dose* **Aspirin**) and:

- ***Low* GI risk** → **Naproxen** + **PPI *or* Misoprostol**.
- ***Moderate* GI risk** → **Naproxen** + **PPI *or* Misoprostol**.
- ***High* GI risk** → **Avoid NSAIDs *or* COX-2 inhibitors**.

Secondary Prevention of NSAID-Induced Ulcers

Recommendations

- ***General recommendations***, *based on* **American College of Gastroenterology** (ACG) **guidelines**;
  - * **Risk factor** ***modification***.
  - * ***Test*** and ***treat*** for *H. pylori*, ***if present***.
  - * ***Discontinue*** or ***lower*** **NSAID dose**, ***if possible***.
  - * ***Drug therapy***;
    1) **PPIs**; ***Drugs of choice***, **Combination product** may be used such as Vimovo® contains **Esomeprazole** with **Naproxen** in the ***same tablet*** (375 mg/20 mg or 500 mg/20 mg).
    2) **Misoprostol**: *effective as* **PPIs** but require ***several*** **doses** *per* **day** and **high doses** *cause* **diarrhea** and **abdominal pain**.
    3) ***Combination*** of a **COX-2 inhibitor + PPI**; may be considered in ***high-risk*** **patients** such as; older adults, especially if they are receiving **Aspirin** plus Steroids or **Warfarin** or have a history of a recent complicated GI event and require continued NSAID or **Aspirin** use.
    4) **H_2RAs**; ***less than*** **Misoprostol** and **PPIs** in ***healing*** and ***preventing*** **recurrence**.

- ***Notes***;
  - Bleeding is also more likely to occur in patients taking NSAIDs who are *H. pylori* positive, the ACG guideline recommends that patients who will be on long-term NSAID therapy be tested for *H. pylori* infection, and eradication therapy should be given if positive.
  - Hemorrhage is the most common complication, with up to 15% of patients experiencing some degree of bleeding.
  - Gastric cancer is the second leading cause of cancer-related mortality. *H. pylori* has an epidemiologic role in the multifactorial process of gastric carcinogenesis.

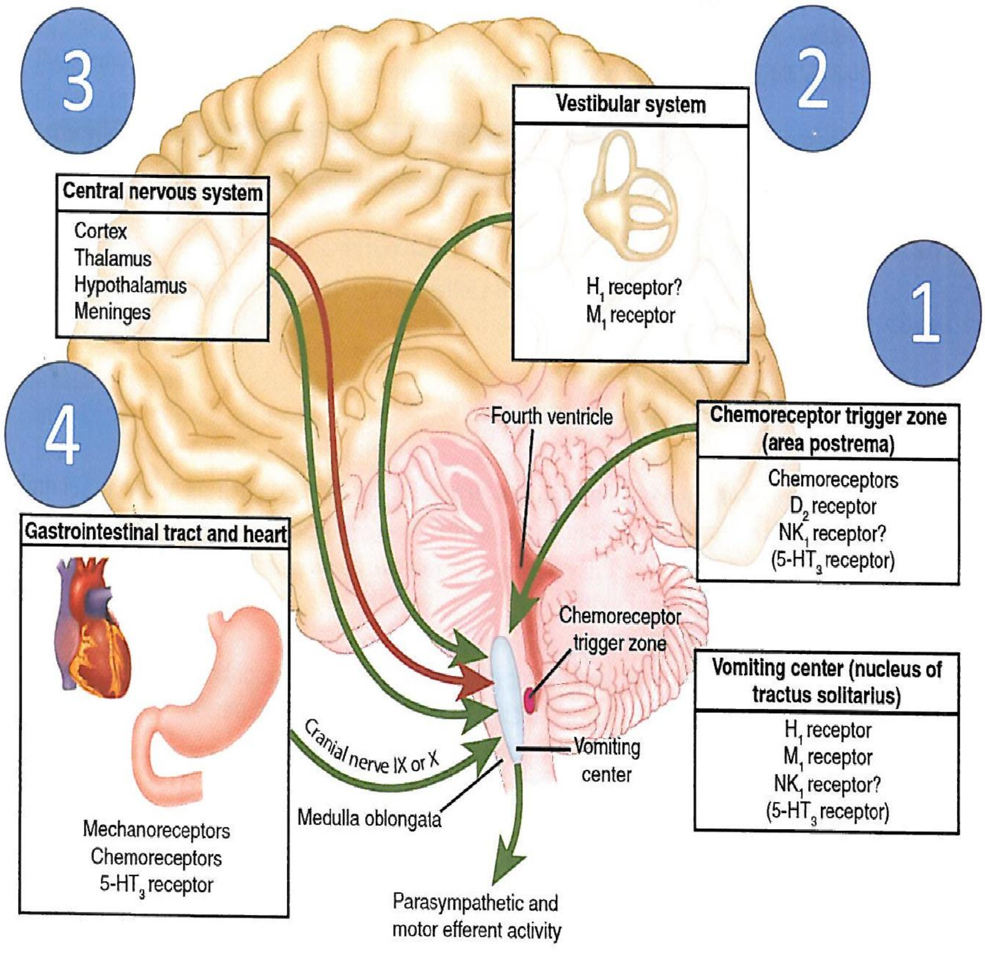
Nausea and Vomiting

➢ Overview:-

- ***Nausea***: ***Unpleasant sensation*** of the ***imminent need*** *to* **vomit**; ***may*** or ***may not*** *lead to* the *act of* **vomiting**.
- ***Vomiting*** (***emesis***): ***Involuntary forceful expulsion*** of **gastric contents** *through the* **mouth**.
- **Nausea** and **vomiting** *may occur* ***separately*** or ***together***.
- **Vomiting** is *different from* **regurgitation**, **regurgitation** is the ***return*** of **undigested food *back*** *up the* **esophagus** to the **mouth**, ***without*** the **force**.
- **Nausea** and **vomiting** may be ***manifestations*** of a ***wide variety of conditions***, *such as*;
  - Adverse effects from medications, radiation or chemotherapy.
  - Systemic disorders, obstructing disorders or infections.
  - Pregnancy.
  - Vestibular dysfunction.

➢ Pathophysiology:-

- The ***three*** **consecutive phases** of **emesis** include **nausea**, **retching** and **vomiting**.
- The ***final phase*** of **emesis** is **vomiting**.
- ***Stimuli*** for **nausea** are ***processed*** *through* **several major anatomic areas**, each of which has *various* **receptors** *associated with* ***input to*** the **medullary vomiting center**.
- There are ***4*** **important sources** of ***afferent input*** to the **vomiting center**:


3
2
1
4
Vestibular system
H_1 receptor?
M_1 receptor
Central nervous system
Cortex
Thalamus
Hypothalamus
Meninges
Fourth ventricle
Chemoreceptor trigger zone (area postrema)
Chemoreceptors
D_2 receptor
NK_1 receptor?
(5-HT_3 receptor)
Gastrointestinal tract and heart
Mechanoreceptors
Chemoreceptors
5-HT_3 receptor
Chemoreceptor trigger zone
Vomiting center (nucleus of tractus solitarius)
H_1 receptor
M_1 receptor
NK_1 receptor?
(5-HT_3 receptor)
Cranial nerve IX or X
Vomiting center
Medulla oblongata
Parasympathetic and motor efferent activity

Neurologic pathways involved in pathogenesis of nausea and vomiting

1) Chemoreceptor Trigger Zone (CTZ)

- *Location*; *located in the* **area postrema**; ***outside*** *the* **blood–brain barrier (BBB)**; can be stimulated by **blood-borne drugs**.
- *Receptors*;
  - *Major*; **Dopamine** (D_2), **Serotonin** (5-HT_3) and **Neurokinin 1**; NK_1 (*receptor for* **Substance P**).
  - *Minor*; **Opioid receptors**. **Histamine** (H_1) and **Muscarinic** (M_1).
- *Major stimuli*;
  - A) **Medications**: **Opiates, dopamine agonists, digoxin, chemotherapeutic agents, macrolides, general anesthetics.**
  - B) **Metabolic disturbances**; **Uremia, diabetic ketoacidosis, hypercalcemia** and **hypoxemia**.
  - C) **Bacterial toxins.**
  - D) **Radiation therapy.**

2) Vestibular System

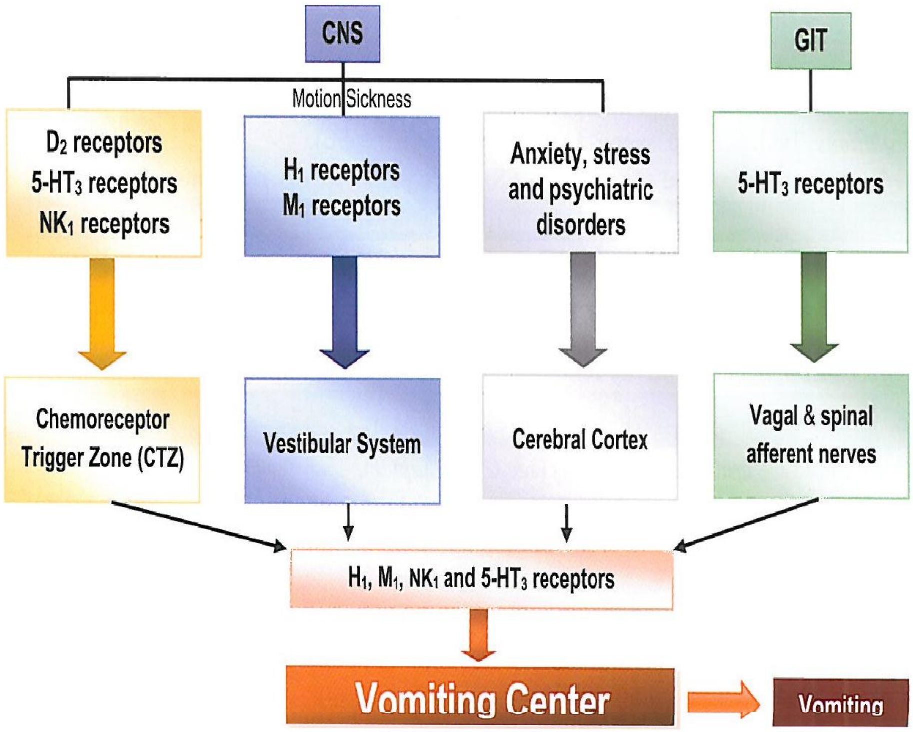
- **Vestibular labyrinths**; is the ***sensory system*** that *provides* ***sense*** of **balance**.
- *Receptors*; ***Rich in*** **Histamine** (H_1) and **Muscarinic** (M_1) ***receptors***.
- *Major stimuli*;
  - A) **Motion sickness.**
  - B) **Labyrinth infection.**

3) Cerebral Cortex

- *Receptor*; ***not well*** **characterized**.
- *Major stimuli*; **Anxiety, psychiatric disorders, stress, noxious odours, visions** and **tastes**.

4) Visceral Stimuli (GIT)

- *Receptors*; **Vagal & spinal afferent nerves** *from* **GIT** are ***rich in*** **Serotonin** (5-HT_3) ***receptors***.
- *Major stimuli*;
  - A) **Gastric irritants (chemotherapy, radiation, distention** or **acute infectious gastroenteritis).**
  - B) **Non-gastric stimuli (peritonitis, intestinal/biliary distension, pancreatitis, gastroparesis).**
  - C) **Pharyngeal stimulation.**


CNS
GIT
Motion Sickness
D₂ receptors
5-HT₃ receptors
NK₁ receptors
H₁ receptors
M₁ receptors
Anxiety, stress and psychiatric disorders
5-HT₃ receptors
Chemoreceptor Trigger Zone (CTZ)
Vestibular System
Cerebral Cortex
Vagal & spinal afferent nerves
H₁, M₁, NK₁ and 5-HT₃ receptors
Vomiting Center
Vomiting

➢ **N.B:-**

- *Nearly* **70-80%** of ***patients*** who undergo **chemotherapy** *experience* **nausea** and/or **vomiting**.
- In **Western societies**, about **50-80%** of **pregnant women** *experience* **nausea** and/or **vomiting** *during* the **first trimester** of **pregnancy** (due to *high levels* **human chorionic gonadotropin**; **hCG**).
- **Uncontrolled vomiting** *can cause*; **dehydration**, **electrolyte disturbances**, **aspiration**, and **Mallory-Weiss syndrome** (upper GI bleeding secondary to longitudinal mucosal lacerations).
- The **overall goal** of **treatment** ***should be*** to ***prevent*** or ***eliminate*** **nausea** and/or **vomiting** ***regardless*** of **etiology**.
- The ***primary goal*** with **chemotherapy-induced nausea and vomiting** (**CINV**) is to ***prevent*** **nausea** and/or **vomiting**.
- **CINV** ***pathophysiology***;
  - ***Centrally*** (*direct*); by ***activate*** **CTZ** or **vomiting center**.
  - ***Peripherally*** (*indirect*); **Chemotherapeutic drugs** can *cause* **cell damage** in the **GI tract** → *release of* **Serotonin** from the **enterochromaffin cells** → *Activates* **5-HT_3 receptors** on **vagal** and **spinal** ***afferent*** **fibers** → *carry* **sensory signals** to the **vomiting center** → **emetic** *response*.

Antiemetic Agents

- ***All*** agents are ***antagonists*** at the **respective receptors**.

Dopamine (D_2) Antagonists

Phenothiazines

- **Phenothiazines** are ***antipsychotic agents*** that can be ***used for*** their ***potent*** **antiemetic** and **sedative** *properties* (*see CNS Chapter*).
- **Phenothiazines** are the ***first group*** of **drugs** *shown* to be ***effective antiemetic agents***.
- ***Antiemetic properties*** of **Phenothiazines** are *mediated through* ***inhibition*** of **dopamine**, **muscarinic** and **histamine** (**H_1**) ***receptors*** *generally* in **CTZ** and **vomiting center**.
- ***Intravenous*** **Phenothiazines** provided ***quicker*** and ***more complete*** **relief** *of* **nausea** and **vomiting** in **adult patients** in an **emergency department**.
- The **agents** ***most commonly*** used as **antiemetics** are **Prochlorperazine** and **Promethazine**.

Prochlorperazine (Compazine®)

- ***Antiemetic mechanism***; *Mainly* **antidopaminergic** ***activity***.
- ***Dose*** of ***antiemetic effect*** is *approximately* a ***third*** of that than its **dose** *for* **psychosis**.
- ***Formulations***; Tablets, syrup, suppositories and injection (*not* SC).
- ***Side effects***; **Extrapyramidal symptoms** (**EPS**) and **hypersensitivity reactions**.

Promethazine (Phenergan®)

- ***Antiemetic mechanism***; **antidopaminergic**, **anticholinergic** and **antihistaminergic** ***activity***.
- ***Formulations***; Tablets, suppositories and injection (*not* SC and IV formulation should be diluted because of risk of tissue necrosis).
- ***Side effects***; **EPS**, **hypersensitivity reactions**, **sedation**, and **anticholinergic effects**.

Butyrophenones

- **Butyrophenone** are ***antipsychotic agents*** (*see CNS Chapter*).
- ***Antiemetic properties*** of **Butyrophenone** are *mediated through* ***block*** of **D_2** ***receptors*** in **CTZ**.
- ***Two*** **Butyrophenone compounds** that have ***antiemetic activity*** are **Haloperidol** and **Droperidol**.

Haloperidol (Haldol®) | Droperidol (Inapsine®)

- ***Formulations***; **Haloperidol**; Injection, tablets. **Droperidol**; Injection.
- ***Side effects***; **Extrapyramidal symptoms** (**EPS**), ***fatal*** **QT prolongation** (ECG monitoring for 2 to 3 hours after administration).
- **Droperidol** in *combination with* **Fentanyl**; used for ***sedation*** in **endoscopy** and **surgery**.

Substituted Benzamides

- **Substituted Benzamides**; are *compounds able to modulate* **dopaminergic receptors**.
- **One** of *several* **Substituted Benzamides** with *antiemetic activity* is **Metoclopramide**.

Metoclopramide (Primperan®)

- **Metoclopramide** is a *peripherally* and *centrally dopamine antagonist*.
- *Formulations*; Tablets, suppositories and injection (*not* SC).
- *Antiemetic mechanism*; *block* **D_2 receptors** in **CTZ**.
- *Side effects*; **extrapyramidal symptoms (EPS)**; *limit long-term use* (can *cause* **tardive dyskinesia**).
- **Metoclopramide** *increases* **lower esophageal sphincter** (**LES**) **tone** and *improve* **gastric emptying**, can be *used in* **gastroesophageal reflux disease** (**GERD**) and **diabetic gastroparesis**.
- It was used as *prophylaxis* for *acute* **chemotherapy-induced nausea** and **vomiting** (**CINV**) *before* the *introduction of* the **5-HT_3 receptor antagonists** (**5-HT_3-RAs**) in the *early* 1990s.
- **5-HT_3-RAs** have *greater* **efficacy** and *decreased* **toxicity** *compared with* **Metoclopramide** in patients who are *receiving* **Cisplatin**-*based* **regimens**.

Other Dopamine (D_2) Antagonists

Domperidone (Motilium®)

- **Domperidone** is a *peripherally dopamine antagonist*.
- *Formulations*; Tablets, suppositories and injection (*not* SC).
- **Domperidone** *may relieve* **nausea** and **vomiting** by *improve* **upper GIT** *motility*.
- **Domperidone** *promote* **lactation** by *blocks* **dopamine receptors** in the *anterior* **pituitary gland** *increasing release* of **Prolactin** which in turn *increases* **lactation**.
- *Side effects*; *Fatal* **QT prolongation** (mostly when used with CYP3A4 inhibitors such as; **Itraconazole** and **Ketoconazole**, **Erythromycin** and *certain other* **macrolide**).

Olanzapine (Zyprexa®)

- **Olanzapine** is an *atypical antipsychotic*, it is *block* **5-HT_{2A}** and **D_2 receptors**.
- **Olanzapine** also *block* **5-HT_3 receptors** *possibly responsible* for its **antiemetic action**.
- **Olanzapine** can be *used* in *combination* with to **standard antiemetics** such as **Palonosetron** and **Dexamethasone**, for *prevent* acute **CINV**.
- **Olanzapine** is **one** of *many options* in patients who *experience* breakthrough **CINV**.

Serotonin 5-HT_3 Receptor Antagonists (5-HT_3-RAs)

Ondansetron (Zofran®) | Granisetron (Kytril®) (EM-EX®) | Palonosetron (Aloxi®)

Dolasetron (Anzemet®) | Tropisetron (Navoban®)

- **Ondansetron** [on-DAN-se-tron], **Granisetron** [gra-NI-se-tron], **Palonosetron** [pa-low-NO-seh-tron], **Dolasetron** [dol-Aseh-tron] and **Tropisetron** [tro-PI-se-tron] are **5-HT_3 receptor antagonist**, *used* to prevent **nausea** and **vomiting** *caused by* **cancer chemotherapy**, **radiation therapy**, **surgery**, or **postoperative** (**Tropisetron** is available outside the USA).
- *Formulations*;
  - **Ondansetron**; Tablet, disintegrating tablet, solution and injection.
  - **Granisetron**; Tablet, solution, patch and injection.
  - **Palonosetron**; Injection (*long duration of action*; 1 to 5 days)
  - **Dolasetron**; Tablets and injection.
- This agents are *off-label used* to treat **morning sickness** & **hyperemesis** in **pregnancy** (category B).
- This agents are *used safely* in **children**.
- *Most common side effects*; **QT interval prolongation** *especially* **Dolasetron** and *high doses* of **Ondansetron** (For this reason, **Dolasetron** is *no longer approved for* **CINV prophylaxis**).

Antihistamines

Diphenhydramine (Dramenex®)	**Cyclizine** (Emetrex®)	**Doxylamine** (Diclegis®)
Dimenhydrinate (Dramamine®)	**Meclizine** (Navidoxine®)	**Promethazine** (Phenergan®)

- **Diphenhydramine** [dye-fen-HYE-dra-meen], **Dimenhydrinate** [dye-men-HYE-dri-nate], **Cyclizine** [SYE-kli-zeen], **Meclizine** [MEK-lizeen], **Doxylamine** [dox-IL-a-meen] and **Promethazine** [proe-METH-a-zeen] are the ***most effective*** **antihistamines agents** for ***prevention*** of the ***symptoms*** of **motion sickness** and **vertigo** (*prevent* **nausea** and **vomiting**), ***used*** 30–60 minutes *before* **travel.**
- **Meclizine** (Navidoxine®), **Cyclizine** (Emetrex®) and **Doxylamine** (Diclegis®) are ***combined with*** **Vitamin B6** (**Pyridoxine**) to ***control*** of **nausea and vomiting of pregnancy** (**NVP**); *first-line treatment* (Diclegis® is pregnancy **category A**, while Navidoxine® and Emetrex® are **category B**).
- Combination of **Doxylamine** & **Vitamin B6** was first introduced in US market as Bendectin® in **1956**
- ***Antiemetic mechanism***; ***due to*** block H_1 & M_1 **receptors** in ***vestibular system*** & may affect at **CTZ.**
- **Diphenhydramine, Dimenhydrinate** and **Promethazine**; ***marked*** **sedation.**
- **Cyclizine** and **Meclizine**; ***slight*** **sedation.**
- **Doxylamine**; ***strong*** **sedation**, ***used*** **insomnia.**
- ***Systemic acute*** **toxicity** of **first-generation antihistamines** are relatively common, ***especially*** in **young children**, including **hallucinations, excitement, ataxia,** and **convulsions.** ***So***, (**Emetrex® Ampoule**) is **NOT** recommended in **CHILDREN** younger than **6 years** to prevent vomiting (***serotonin antagonists*** such as **Ondansetron** is safer).

Antimuscarinic

Scopolamine or Hyoscine (Transderm Scop®)

- **Scopolamine** [skoe-POL-a-meen] is a ***prototypic*** **muscarinic receptor antagonist**, is **one** of the ***best agents*** for the ***prevention*** of **motion sickness.**
- It also ***used in postoperative*** **nausea and vomiting.**
- ***Formulations***; **topical patch** that **provides effects** for ***up to*** **3 days.**

Benzodiazepines

Diazepam (Valium®)	**Lorazepam** (Ativan®)
Alprazolam (Xanax®)	**Midazolam** (Dormicum®)

- **Diazepam** [dye-AZ-e-pam], **Lorazepam** [lor-AZ-e-pam], **Alprazolam** [al-PRAY-zoe-lam], **Midazolam** [mi-DAY-zoe-lam] are **benzodiazepine agents.**
- The ***antiemetic potency*** of **benzodiazepines** is ***low.***
- The ***beneficial effects*** may be *due to* their **sedative, anxiolytic,** and **amnesic** *properties.*
- This agents may ***useful*** in ***anticipatory*** **vomiting** *such as* in **initiation of chemotherapy.**
- ***Concomitant use*** of **alcohol** ***should be*** **avoided** due to ***additive*** **CNS depressant effects,** ***particularly*** at **high doses,** may ***produce*** **unconsciousness, respiratory depression,** and even **death.**

Corticosteroids

Methylprednisolone (Depo-Medrol®)	**Dexamethasone** (Epidron®)

- **Dexamethasone** [dex-a-MEH-tha-sone] and **Methylprednisolone** [meth-ill-pred-NIH-so-lone] are ***used*** in ***prevention*** of ***acute*** and ***delayed*** **nausea** and **vomiting** in ***patients receiving moderately*** to ***highly*** **emetogenic chemotherapy** *regimens.*
- It ***may use*** in ***combination*** with *other* **antiemetic agents.**
- **Dexamethasone**; 8-20 mg IV before chemotherapy, followed by 8 mg/d orally for 2–4 days, is ***commonly*** **administered.**
- **Corticoadrenal Extract** + (**Pyridoxine**) **Vitamin** B_6 (Cortigen-B_6®) *was available* to ***control*** **nausea** and **vomiting** in and ***may use*** *during* **pregnancy** or in **children** or **pediatrics.**

Cannabinoids

Dronabinol (Marinol®)	**Nabilone** (Cesamet®)

- **Nabilone** [NAB-i-lone] and **Dronabinol** [droe-NAB-i-nol] are a synthetic Δ^9-**Tetrahydrocannabinol (THC)** ***analog***, ***used*** in **severe** **nausea** and **vomiting** *caused by* **cancer chemotherapy** (CINV).
- Can be ***used to*** **stimulate appetite** in ***patients with*** AIDS.
- *May* cause **euphoria, cognitive impairment.**
- ***Combination therapy*** with **Phenothiazines** ***provides*** **synergistic antiemetic action** and appears to ***attenuate*** the **adverse effects** of ***both*** **agents.**

Neurokinin 1 (NK$_1$) Receptor Blockers

Aprepitant (Emend®)	**Netupitant** (Akynzeo®)	**Rolapitant** (Varubi®)

- **Aprepitant** [a-PRE-pi-tant] is the ***first*** **Neurokinin 1** (NK$_1$) **receptor blocker**, it was FDA approved in 2003, is available in ***oral formulation***.
- **Aprepitant** is *usually* ***combined*** with **Dexamethasone** and a **5-HT$_3$** ***antagonist*** in ***preventing*** CINV.
- **Fosaprepitant** [FOS-a-PRE-pi-tant] is an **IV form** of **Aprepitant**, *converted to* **Aprepitant** ***within*** **30 minutes** *after* **infusion.**
- **Netupitant** [net-UE-pi-tant] was ***approved in*** **combination** with **Palonosetron**; Akynzeo® in ***preventing*** CINV.
- **Rolapitant** [roe LA pi tant] is approved in ***combination*** with ***other*** **antiemetic agents** in ***adults*** for the ***prevention*** of ***delayed*** **nausea** and **vomiting associated** with ***initial*** and ***repeat courses*** of **emetogenic cancer chemotherapy**, ***including, but not limited to***, **highly emetogenic chemotherapy.**
- ***Drug interactions***; **NK$_1$ receptor blocker** are **CYP3A4** ***inhibitors*** (**warfarin** and **oral contraceptives**).
- ***Contraindications***; ***severe*** **renal** or **hepatic disease.**

Others

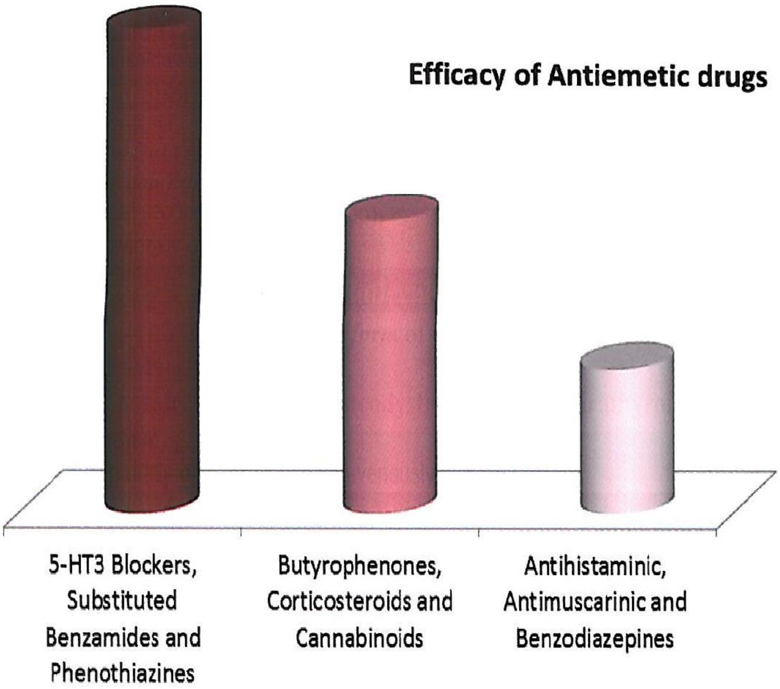
Ginger

- **Ginger** (*Zingiber officinale*) **root** or *simply* **ginger**, is *widely used* as a **spice** or in **medicine.**
- **Ginger** has a *long history* as an **anti-nausea** ***activity***, may *due to* ***peripheral*** **anticholinergic** and **antiserotonin** ***actions*** on GIT, It may ***use*** to ***relieve*** **nausea** and **morning sickness** *during* **early pregnancy** (**NVP**).
- ***Fresh*** **ginger** or **ginger** ***teas*** or in ***capsules*** or ***tablets*** are *often used. However*, it depends how ***sensitive*** to **smells & flavours** and may **make symptoms** ***worse*** or if **women** have **heartburn.**

Glucose/Fructose/Phosphoric acid (Emetrol®)

- **Glucose/fructose/phosphoric acid** (Emetrol®) or **phosphorylated carbohydrate solution** is an ***OTC antiemetic*** used to ***relieve*** **nausea** and **vomiting.**
- Can be ***used*** in **NVP** and **children.**
- ***Contraindicated*** in **diabetes** and **fructose intolerance.**

➢ Antiemetic Activity:-



➢ Combination Regimens:-

- ***Antiemetic drugs*** are often *combined* to ***increase*** **antiemetic activity** or ***decrease*** **toxicity**;
  - **Corticosteroids** *such as* **Dexamethasone**, ***increase*** **antiemetic activity** when given with ***high-dose*** **Metoclopramide**, a **5-HT$_3$ antagonist**, **Phenothiazine**, **Butyrophenone**, or **Benzodiazepine**.
  - **Antihistamines**, *such as* **Diphenhydramine**, are often administered in ***combination with high-dose*** **Metoclopramide** to ***reduce*** **extrapyramidal reactions** or with **Corticosteroids** to *counter* **Metoclopramide**-*induced* **diarrhea**.
- **Best regimen for CINV**; is a **three-drug combination** of a **5-HT$_3$ antagonists**, a **glucocorticoid**, and **Aprepitant**; prevents acute emesis in 80 to 90% of patients and prevents delayed emesis in more than 70% of patients; American Society of Clinical Oncology guidelines in antiemetics in oncology.

➢ Treatment and Prevention Strategies:-

1) ***Removal*** or ***treatment*** of the **underlying cause**.
2) ***Correction*** of **dehydration** and **electrolyte disturbances** (oral rehydration, if possible).
3) **Drug treatment**:
   - Use drugs that target receptors involved with stimuli.
   - May need combination of drugs with different mechanisms.
   - Also may need alternative dose forms (intravenous, subcutaneous, suppository).

*** ***Drugs of choice for different situations include***:

- ***General medical use***: **Phenothiazines** and **Serotonin antagonists.**
- ***Chemotherapy induced***: **Serotonin antagonists**, **Phenothiazines**, **Aprepitant** & **Dronabinol.**
- ***Postoperative***: **Serotonin antagonists** and **Scopolamine.**
- ***Motion sickness***: **Antihistamines** and **Scopolamine.**
- ***Pregnancy***: **Pyridoxine**, **Antihistamines**, **Ginger** & **phosphorylated carbohydrate solution.**
- ***Gastroparesis***: **Metoclopramide.**

Diarrhea

➢ Overview:-

- **Diarrhea** [dia-rrho-ea] or **Diarrhoea**; is ***characterized by*** **loose, watery stools** or a ***frequent*** **need to *have* a bowel movement.**
- **Diarrhea** *remains* the ***second*** *leading* **cause of mortality *after* pneumonia** in ***infant***.
- ***Most common*** **cause** is an **infection** of the ***intestines*** (**virus, bacteria** or **parasite**).
- ***Viral diarrhea*** is ***most common*** in **young children** (*rotavirus* and *astrovirus*).
- ***Management of diarrhea*** *focuses on* ***preventing*** *excessive* **water** and **electrolyte** *losses*, **dietary** *care*, ***relieving*** **symptoms**, ***treating*** **curable causes**, and ***treating*** **secondary disorders**.

➢ Definitions:-

- *Alteration in* a ***normal*** **bowel movement** ***characterized by*** an ***increase in*** the **water content, volume,** or **frequency** (***more than 3*** *per* **day**) of **stool**.
- ***Acute Diarrhea***; ***Less than*** **14 days**.
- ***Chronic*** (or ***Persistent***) ***Diarrhea***; ***More than*** **14 days**.

➢ Signs and Symptoms:-

- ***Abrupt onset of*** **nausea**, **vomiting**, **abdominal pain**, **headache**, **fever**, **chills** and **malaise**.
- ***Bowel movements*** are **frequent** and **never bloody**, and **diarrhea** lasts 12 to 60 hours.
- ***In chronic diarrhea***; **dehydration**, **weight loss**, **anorexia**, and **chronic weakness**.

➢ Classification:-

1) Secretory Diarrhea

- ***Mechanism***; ***Secondary*** to ***enhanced*** **secretion** by **intestinal mucosa**.
- ***Stool***; ***Often***, **large, watery volume** with ***loss*** of **electrolytes**.
- ***Common causes***; **bacterial** or **viral enteritis**, **gastric hypersecretion**, **carcinoid**, **stimulant laxatives**, **bile acid malabsorption**, **celiac disease** and **mucosal inflammatory bowel disease** (**IBD**).

2) Osmotic Diarrhea

- ***Mechanism***; ***Secondary*** to the **presence** of **hyperosmolar gradient** in the **intestinal lumen**.
- ***Common causes***; **osmotic laxatives**, **carbohydrate malabsorption** (*lactase deficiency*), **fat malabsorption** (*pancreatic insufficiency*), **short bowel syndrome**.

3) Exudative (or Inflammatory) Diarrhea

- ***Mechanism***; ***Secondary*** to **inflammation** or **infiltration** or **invasion** of the **intestinal mucosa**.
- ***Common causes***; **IBD**, **invasive infection** (*Clostridium difficile* toxin, enterotoxigenic *Escherichia coli*, cytomegalovirus, *Shigella*), **ischemic colitis**, **radiation enterocolitis** and **neoplasm**.
- **Dysentery**; is a *type of* **gastroenteritis** that *results in* **diarrhea** with **blood**, caused by a number of types of infection such as **bacteria**, **viruses**, **parasitic worms**, or **protozoa**.

4) Altered Motility (or Motor) Diarrhea

- ***Mechanism***; ***Secondary*** to **autonomic nerve dysfunction**.
- ***Common causes***; **diabetic neuropathy**, **postvagotomy**, **hyperthyroidism**, **irritable bowel syndrome** (**IBS**), **Addison disease**.

- ***N.B.***: **Traveler's Diarrhea** (**TD**); is an **acute diarrhea** *caused by* **eating** ***contaminated*** **food** or **drinking**, ***when*** **traveling**.

➢ Common Causes of Drug-Induced Diarrhea:-

- **Antibiotics**
- **Chemotherapy**
- **Laxatives**
- **NSAIDs**
- **Prostaglandins** (Misoprostol)
- **Colchicine**
- **Levothyroxine**
- **Digoxin**
- **Metoclopramide**
- **Orlistat** (*used in obesity*)
- **Acarbose** or **Miglitol** (*oral anti-diabetic*)
- **Sorbitol** (*sugar alcohol*)

➢ Diagnosis:-

- *History*;
  - **Stool characteristics** (e.g.; consistency, color, volume, frequency).
  - **Presence of associated enteric symptoms** (e.g.; nausea/vomiting, fever, abdominal pain).
  - **Use of child day-care** (*common pathogens*: rotavirus, astrovirus, calicivirus; *Campylobacter*, *Shigella*, *Giardia*, and *Cryptosporidium* species).
  - **Food ingestion history** (e.g.; raw/contaminated foods, food poisoning)
  - **Water exposure** (e.g.; swimming pools, marine environment)
  - **Camping history** (possible exposure to contaminated water sources)
  - **Travel history** (common pathogens affect specific regions; also consider rotavirus and *Shigella*, *Salmonella*, and *Campylobacter* spp regardless of specific travel history, as these organisms are prevalent worldwide)
  - **Animal exposure** (e.g.; young dogs/cats: *Campylobacter* spp; turtles: *Salmonella* spp).
  - **Predisposing conditions** (e.g.; hospitalization, antibiotic use, immunocompromised state).
  - **Drug-induced diarrhea** (e.g.; laxative, recent antibiotic use).
- *Lab tests*;
  - **Stool culture, stool pH, electrolytes, osmolarity** or **fat content.**
  - **CBC**, **fluid** and **electrolyte status.**
  - **Imaging** (abdominal CT scan) or **endoscopy** ***with*** **biopsy** may be indicated.

➢ Patients Who Need Higher Level of Care or Further Evaluation:-

- **Infants and children.**
- **Pregnant women.**
- **Presence of fever.**
- **Blood in the stool.**
- **Weight loss** (*greater than 5%*).
- **Suspected invasive infection.**

➢ Treatment Strategies:-

A) ***Removal*** or ***treatment*** of **underlying causes**, if possible.

B) **Rehydration**;

1) **IV fluids** *for* **hospitalized patients.**
2) **Oral rehydration** *for all* **patients** *if* ***no*** **vomiting**;

Oral Rehydration Therapy (ORT) (Rehydran-N®)

- **ORT** is a *type of* **fluid replacement** used to ***prevent*** or ***treat*** **dehydration** ***especially*** *due to* **diarrhea.**
- **Risk** of ***dehydration*** is ***greatest in*** **babies**, and **rehydration therapy** is the ***standard*** **treatment** for **diarrhea** in **babies** and **young children**, and may use in **adults**.
- **ORT** ***usually*** used *with* **antidiarrheal.**
- **Sodium** and **Glucose** are ***key ingredients*** of **oral rehydration solutions** because they have ***active uptake*** into the **intestinal mucosa** *even during active* **diarrhea**. This ***results in*** **water** being ***pulled back*** *into* **circulation**.
- ***Dose*** **and** ***Administration*** (Rehydran-N®);
  - ***Dissolve*** the **content** of this **sachet** in **200 ml** of **water** (glass of water) to *form* **Oral Rehydration Solution** (**ORS**).
    - For ***prevention*** of **dehydration**: Give 50 ml solution per stool motion.
    - For ***treatment*** of **dehydration**: Give the solution to the child to drink as he or she can, and continue breast feeding or normal feed.

C) Dietary modifications;

- *Avoid* **dairy products**; transient lactase deficiency may occur (decrease ability to digest lactose).
- **BRAT diet** *for* ***adults***;
  - **BRAT diet**; is a diet can be used for people with **vomiting**, **diarrhea** or **gastroenteritis**.
  - **BRAT** is a *mnemonic for* **B**ananas, **R**ice, **A**pple sauce and **T**oast.
  - **BRAT diet** may *help* ***reduce*** the ***possibility*** of **dehydration**.
  - **BRAT diet** may not be the ***best option*** for **children** *during* **illness**, *because* **BRAT** ***lacks*** **enough nutrition** to *help* a **child's GIT** ***recover***.

D) Antimicrobial Agents; *see chemotherapy chapter for full illustration*.

- **Antimicrobial agents** help to ***treat*** **diarrhea** *caused by* **bacteria** or **parasites**.
- ***Most common*** **antimicrobial agents** *used in* **diarrhea**;

Antibiotics

- **Cefixime** (Suprax®); is a ***potent*** *long-acting* **oral** ***third generation cephalosporin*** with *increased* **gram-negative coverage**.
- **Ceftriaxone** (Rocephin®) and **Cefotaxime** (Claforan®); are ***potent*** **injectable** ***third generation cephalosporin*** with *increased* **gram-*negative* coverage** and ***some* gram-*positive*** **bacteria**.
- **Fluoroquinolone antibiotics**; *such as* **Ciprofloxacin** (Cipro®) and **Levofloxacin** (Tavanic®); ***Drug of choice*** for **traveler's diarrhea** in *most parts* of the **world**.
- **Azithromycin** (Zithromax®); is a **macrolide antibiotic**, is also a ***good choice*** in **traveler's diarrhea** for **pregnant women** and **children** and for patients who ***cannot*** otherwise tolerate **Quinolone antibiotics**.
- **Rifaximin** (Xifaxan®); Used in ***non-invasive*** (*non-bloody*) **traveler's diarrhea** caused by *E. coli*.
- **Sulfamethoxazole/Trimethoprim** (Septrin®) known as **Co-Trimoxazole**; Can be used in **traveler's diarrhea** ***prophylaxis***.
- **Vancomycin** (Vancocin®); ***Used orally*** for **antibiotic-associated colitis** (**pseudomembranous colitis**) due *Clostridium difficile*.
- **Doxycycline** (Vibramycin®); is a ***good choice*** for *Vibrio cholerae* infection and Can be used in **traveler's diarrhea** ***prophylaxis***.
- **Neomycin** (*not absorbed from GIT*) and **Streptomycin**; are an **aminoglycoside antibiotic** can be used ***orally*** in **traveler's diarrhea**.
- **Bismuth Subsalicylate** (Pepto-Bismol®); Used in **traveler's diarrhea** ***prophylaxis***.
- **Nifuroxazide** (Antinal®); is an **oral** ***nitrofuran antibiotic***, is a ***broad spectrum*** **intestinal antiseptic** for the *treatment* of **diarrhea** & **gastroenteritis** (*poorly absorbed from the GIT, act mainly locally*).

Antiprotozoal

- **Nitazoxanide** (Alinia®); Used in **diarrhea** caused by *Cryptosporidium parvum* (**Cryptosporidiosis**) or *Giardia lamblia* (**Giardiasis**).
- **Metronidazole** (Flagyl®); is an ***antibiotic*** and ***antiprotozoal agent***, it is effective against wide range of microorganisms, is a ***good choice*** for **diarrhea** caused by; *Entamoeba histolytica* (**Amoebic dysentery** or **Amebiasis**), *Clostridium difficile* (**antibiotic-associated colitis**), *Giardia lamblia* (**Giardiasis**).
- **Tinidazole** (Fasigyn®), **Secnidazole** (Flagentyl®) and **Ornidazole** (Tibezole®); are an ***antibiotic*** and ***antiprotozoal agent*** like **Metronidazole**.

Antiparasitic

- **Albendazole** (Alzental®), **Mebendazole** (Antiver®) and **Flubendazole** (Fluvermal®): is a ***broad spectrum*** **anthelmintic agents** used in **diarrhea** *caused by* **worms**.

E) Antidiarrheal Agents;

Antimotility Agents

- **WARNING**; - *Avoid* **antimotility agents** in **infection** (*presence of high fever*).
  - *Avoid* **antimotility agents** in **bloody stool**.

Loperamide (Imodium®)

- **Loperamide** [loe-PER-ah-mide] is an **OTC opioid drug**, act as **μ receptor *agonist*** on ***large intestine*** (*does not cross the BBB*), ***Concurrent* administration** of **P-glycoprotein *inhibitors*** (*mechanism prevents* **Loperamide** *from crossing the BBB*) such as **Quinidine** allow **Loperamide** to cross the BBB, and may produce **respiratory depression**.
- **Loperamide** is effective for the ***treatment*** of a ***many types*** of ***non-invasive*** **diarrhea**.
- ***Pregnancy***; **Category B**.
- ***Side effects***; it *may* ***increase* risk** of **toxic megacolon** (*acute colonic distension*) and **paralytic ileus**.
- ***Contraindications***; ***high*** **fever**, ***bloody*** or ***black*** **stool** and in **children > 2 years**.

Diphenoxylate/Atropine (Lomotil®)

- **Diphenoxylate** [dye-fen-OX-see-late] is a ***prescription*** **opioid drug**, act as **μ receptor *agonist*** (cross BBB and may cause **physical dependence** with high doses).
- **Atropine** [AT-row-peen] is an ***anticholinergic agent***, *added in* this ***combination*** to **discourage abuse** (the **anticholinergic effect** of **Atropine** will produce ***severe weakness*** and ***nausea*** [**atropinism**] if **standard dosage** is ***exceeded***).
- ***Pregnancy***; **Category C**.
- ***Side effects***; ***Atropine like effects*** (dry mouth, headache and blurred vision).
- ***Overdose***; **convulsions** and **respiratory depression**.
- ***Contraindications***; ***high*** **fever**, ***bloody*** or ***black*** **stool** and in **obstructive jaundice**.

Antisecretory Agents

- **These agents** *act by* ***reduce*** the **amount** of **water** that is ***released into*** the **gut** *during* **diarrhea**.

Bismuth Subsalicylate (Pepto-Bismol®)

- **Bismuth Subsalicylate** [BIZ-muth sub-sa-LIS-a-late] *appears to have* **antisecretory**, **anti-inflammatory**, and **antibacterial *effects***.
- It also available as **OTC drug** for **indigestion**, ***relieving*** **abdominal cramps**, **peptic ulcer *healing***, and ***controlling*** **diarrhea**, *including* **traveler's diarrhea**.
- **Bismuth Subsalicylate** ***reducing*** the **number** of **unformed stools** by *approximately* **50%**.

Adsorbent Agents

- **These agents** *act by* ***adsorbing*** (***binding***) **intestinal toxins** or **microorganisms** and/or by ***coating*** or ***protecting*** the **intestinal mucosa**.

Aluminum Hydroxide [$Al(OH)_2$]

- **Aluminium hydroxide** is an ***antacid***, and ***less commonly used*** in **diarrhea**.

Attapulgite (Rheaban®)

- **Attapulgite** [at-a-PUL-gite] is a **Magnesium Aluminium Phyllosilicate** which found in a type of clay soil in South-eastern United States, act by ***binds*** to **bacteria** & **toxic substances** in **GIT**.

Methylcellulose (Citrucel®)

- **Methylcellulose** [meth-ill-CELL-you-lowse] is ***not absorbed***, is a ***hydrophilic colloid*** which ***absorbs*** **water** in the **intestines**.

Kaolin-Pectin (Kapect®)

- **Kaolin/Pectin** [KAY-oh-lin/PECK-tin] ***mixture*** is an off-white ***suspension used for*** **diarrhea**.
- **Kaolin**, is a ***natural*** **hydrated aluminum silicate**, ***not absorbed***, act by ***binds*** to **bacteria** and **toxic substances** in the **GIT**.
- **Pectin** is a ***polyuronic polymer*** extracted from **citrus fruits**, the **mechanism of action** is *unknown*, but it may ***decrease*** **stool softness (stool modifiers)** and ***increase*** **viscosity**.

F) Alternative Therapies;

Lactase Enzyme

- **Lactase** [LAK-teys] is an ***enzyme*** that ***aids*** in the ***digestion*** of **Lactose**.
- **Lactose** is in ***dairy foods***, this ***enzyme supplement*** is used to ***break down*** **Lactose** and ***prevent*** **bloating**, **diarrhea**, and **gas** of **lactose intolerance**.
- **Lactase** ***enzyme used*** in **lactose intolerance patient** ***taken with*** **milk** or **dairy product**.

Probiotics (Bacterial Replacement Therapy) (Lacteol® forte)

- **Probiotics** are ***microorganisms*** that have been **used** for ***many years*** (1985) to *replace* **colonic microflora** (as a result of screening bacteria in fermented milk products thought to be beneficial to human health).
- **Probiotics** ***restores*** *normal* **intestinal function** and *suppresses* the ***growth*** of **pathogenic microorganisms**.
- *Saccharomyces boulrdii*, *Lactobacillus GG*, and *Lactobacillus acidophilus* have been shown to ***decrease*** the **duration** of **infectious** and **antibiotic-induced diarrhea** (*C. difficile*) in ***adults*** and ***children*** (*Not used in severely immunocompromised patients*).

Zinc

- **Zinc** is ***important for*** **cellular** ***growth***, **cellular** ***differentiation*** and **metabolism** and ***deficiency*** **limits childhood growth** and ***decreases*** **resistance** *to* **infections**.
- **Zinc supplementation** has been shown to ***reduce*** the **duration** and **severity** of **diarrhea**, and to ***prevent*** **subsequent episodes**.
- ***WHO recommendations***; Mothers, other caregivers and health workers should provide children with 20 mg per day of **Zinc supplementation** for 10-14 days (10 mg per day for infants under the age of six months).

F) Other Therapies;

Cholestyramine (Questran®)

- **Bile acid sequestrants** *such as* **Cholestyramine** [KOE-le-STYE-ra-meen] is ***used*** in **chronic diarrhea** ***due to*** **bile acid malabsorption** (*binds bile in the GIT to prevent its reabsorption*).

Octreotide (Sandostatin®)

- **Octreotide** [ok-TREE-oh-tide] is a ***synthetic octapeptide analog*** of ***endogenous*** **Somatostatin**.
- **Somatostatin** ***hormone*** is *classified as* an ***inhibitory hormone***: ***Inhibits release*** of **numerous hormones**, *such as*; **gastrin**, **insulin**, **growth hormone** (**GH**), **vasoactive intestinal peptide** (**VIP**), **thyroid stimulating hormone** (**TSH**), **gastrointestinal hormones** and **pancreatic hormones**.
- **Somatostatin** is ***limited to use*** *due to* its ***short*** **half-life** in the **circulation** (3 minutes), **Octreotide** *similar to* **Somatostatin**, but ***long*** **duration of action**.
- ***Uses***; **tumor associated diarrhea** (carcinoid tumor and vasoactive intestinal peptide tumors "*VIPomas*" cause watery diarrhea and systemic symptoms such as flushing and wheezing), and **chemotherapy-induced diarrhea** and **AIDS-associated diarrhea**.
- ***Other uses***; **Acromegaly** (GH producing tumor) and **esophageal varices bleeding**,
- ***Side effects***; **GIT side effects** (cramps, nausea/vomiting and diarrhoea or constipation) **Gallstones**, **hyperglycemia** or **hypoglycemia** (hyperglycemia is less frequently and usually mild) and **hypothyroidism**.

Teduglutide (Gattex®)

- **Teduglutide** [TE-due-GLOO-tide] is **glucagon-like peptide-2** (**GLP-2**) ***analogue***.
- ***Uses***; ***treatment of*** **short bowel syndrome** (**SBS**) in ***patients who receive*** **IV feeding**.
- Short bowel syndrome (SBS) is a malabsorption disorder caused by a lack of functional small intestine. The primary symptom is ***diarrhea***, which can result in dehydration, malnutrition, and weight loss.
- ***Mechanism***; acts by ***increasing*** **blood flow** to the **bowels**. This ***increases*** the ***flow of*** **water**, **electrolytes**, and **nutrients** *into the* **bowels**, which ***reduces*** the *need for* **IV feeding**.

Side effects; **GIT side effects, respiratory infections, injection site reactions, and headache.**

Constipation

➢ Overview:-

- **Constipation** is the ***most common*** **digestive complaint** in the **United States.**
- **Constipation** ***refers to*** **bowel movements** that are ***infrequent*** or ***hard to pass.***
- **Constipation** is a **symptom** ***rather than*** a **disease.**
- **Constipation** is ***generally*** *described as* having ***less than*** **3 bowel movements** a ***week.***
- *Chronic* **constipation** is ***infrequent*** **bowel movements** or ***difficult*** **passage of stools** that ***persists*** for ***several*** **weeks** or **longer.**
- *Severe* **constipation** includes **obstipation** (failure to pass stools or gas) and **fecal impaction**, which can progress to ***bowel obstruction*** and *become* **life-threatening.**

➢ Definitions:-

- The **definition** of **constipation** *includes* the ***following***;
  * **Infrequent bowel movements** (*typically* **less than** 3 **times** ***per*** **week**).
  * **Straining** ***during*** **bowel movements** (***difficulty*** *during* **defecation**).
  * ***Sensation*** of **hard dry stools.**
  * ***Sensation*** of ***incomplete*** **defecation.**

- **Patients** may **complain** ***one*** or ***more*** of the *following*:
  * **Abdominal bloating.**
  * **Pain on defecation.**
  * **Rectal bleeding.**
  * **Low back pain.**

➢ Classifications and Causes:-

1) Primary (or functional) Constipation

- **Primary constipation** is ***not*** *due to* any **underlying cause** such as **medication side effects** or an **underlying medical condition.**
- Is the ***most common*** cause and ***not*** **life-threatening.**
- **Primary** (or ***functional*** or ***idiopathic***) **constipation** can generally be ***subdivided*** into the following **3 types:**
  - A) **Normal-transit constipation** (**NTC**); **stool** ***passes*** *through the* **colon** at a **normal rate.**
    - ***Most common*** **subtype.**
    - ***Difficult*** to ***evacuate*** **bowels.**
    - ***Normal*** **physical examination.**
    - ***Not associated*** *with* **abdominal pain**, thus ***distinguishing it*** *from* **irritable bowel syndrome** with **constipation** (**IBS-C**).
  - B) **Slow-transit constipation** (**STC**); **stool** ***passes*** *through the* **colon** at a **slow rate.**
    - ***More common*** in **female.**
    - ***Infrequent*** **bowel movement.**
    - ***Decreased*** **urgency**, or **straining** to *defecate.*
  - C) **Pelvic floor dysfunction**; ***dysfunction*** of the **pelvic floor** or **anal sphincter.**
    - ***Prolonged*** or ***excessive*** **straining.**
    - ***Feeling*** of ***incomplete*** **evacuation.**
    - **Use** of **perineal** or **vaginal** ***pressure*** *during* **defecation** to ***allow*** the **passage** *of* **stool.**

2) Secondary Constipation

- **Constipation** can be ***caused*** or ***exacerbated*** *by*;
  - A) **Diet**; Low-fiber diet, low liquid intake, dieting or overuse of coffee and tea may cause constipation.
  - B) **Metabolic** or **Hormonal**; Pregnancy, Diabetes, hyperparathyroidism and hypothyroidism.
  - C) **Structural** (morphological or anatomical); Colon cancer, anal fissures, proctitis (inflammation of the anus and the lining of the rectum), and pelvic floor dysfunction.
  - D) **Neurological**; Autonomic neuropathy, Multiple sclerosis, Parkinson's disease, Spinal cord injury, Hirschsprung's disease and Stroke.
  - E) **Psychological**; Stress, Depression and Anxiety.
  - F) **Medications**;
    - **Opioids**
    - **Scopolamine**
    - **Bile acid sequestrants**
    - **Aluminum**-*containing drugs*
    - **Benzodiazepines**
    - **Antihistamines**
    - **Benztropine**
    - **Calcium channel blockers**
    - **Iron** *supplements*
    - **Phenothiazines**
    - **Tricyclic antidepressants**
    - **Diuretics**
    - **Calcium** *supplements*
    - **Antacids** (Al, Ca)

➢ Complications:-

- *Complications* of **chronic constipation** *include*: **Rectal bleeding, anal fissure, hemorrhoids, faecal impaction and rectal prolapse.**

➢ Diagnosis:-

- *History*;
  - **Patient's symptoms** *description* (see definition).
  - ***Other symptoms***; bloating, distension, abdominal pain (IBS-C), low back pain, headaches and fatigue.
- *Physical examination*;
  - **Rectal examination**; anatomical abnormalities (fistulas, fissures, hemorrhoids, rectal prolapse) and colonoscopy
  - **Abdomen examination**; X-rays (if bowel obstruction).
- *Lab tests*;
  - **Fluid** and **electrolyte**.
  - **Thyroid function test**.

- *Diagnostic criteria*;
  - **Rome III diagnostic criteria for constipation**;
    - A) **Must include** *2* or ***more*** of *the following*;
      - *) Less than 3 defecations per week.
      - *) Straining during at least 25% of defecations.
      - *) Lumpy or hard stools in at least 25% of defecations.
      - *) Sensation of incomplete evacuation for at least 25% of defecations.
      - *) Sensation of anorectal obstruction/blockage for at least 25% of defecations.
      - *) Manual maneuvers to facilitate at least 25% of defecations.
    - **B)** Loose stools are rarely present without the use of laxatives.
    - **C)** Insufficient criteria for irritable bowel syndrome.
    - * Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

"Rome process" is an international effort to create scientific data to help in the diagnosis and treatment of functional gastrointestinal disorders (FGIDs)

➢ Treatment Strategies:-

- A) *Removal* or *treatment* of **underlying causes**, if possible.
- B) **Non-pharmacologic Therapy**;
  - 1) ***Increase*** **fluid intake** to **6-8 glasses** of **water** ***per*** **day**; *stool softness*.
  - 2) ***Increase*** **dietary fiber** to **20-30 g/day** (fruits, vegetables and cereals); bulk forming.
  - 3) ***Incorporate*** or ***increase*** **exercise** to 3–5 days/week; *stimulate intestinal activity*.

C) Pharmacological Therapy;

Laxatives

➢ Terminology:-

- **Laxatives**, **Purgatives** & **Cathartics** are terms describing **drugs** that ***promote*** **evacuation** of the **intestine**.

	Laxatives +	Purgatives ++	Cathartics +++
Potency	Powerful	More powerful	Most powerful
Action	Eases defecation	Accelerates defecation	Urgency defecation
End-Stool	Soft stool	Liquefied stool	More liquid stool
Example	**Psyllium**	**Bisacodyl**	**Magnesium Sulfate**

- **Laxatives**, **Purgatives** & **Cathartics** will be *easily* **referred to** as **Laxatives.**

Stimulant (or Irritant) Laxatives

- **Stimulant laxatives** are ***substances*** that act on the **intestinal mucosa** or **enteric nervous system**, ***altering*** **water** and **electrolyte** ***secretion*** and ***stimulate*** **peristaltic action.**
- ***Long-term use*** of **stimulant laxatives** *could lead to* **dependence** and ***destruction*** of the **myenteric plexus**, resulting in **colonic atony** and **dilation.**

Senna (Senokot®)

- **Senna** [SEN-nah] is **naturally occurring** ***from*** *Senna* **plant**, it has been **used** *at least* since the **700s** AD (Anno Domini).
- **Senna** is ***widely used*** **stimulant laxative**.
- ***Active ingredient***; **Sennoside** [SEN-oh-side] is an ***anthraquinone glycoside.***
- ***Uses***; - ***Short-term*** **relief of** ***acute or intermittent*** **constipation.**
  - ***Evacuation*** of the **bowel** *before* **surgery** or **colonic examinations.**
  - ***Prevention*** of **opioid-induced constipation.**
- ***Formulations***; **oral formula** and **suppository.**
- ***Administration***; **orally**; ***once daily*** at **bedtime.**
- ***Onset***; **6-12 hours** *when given* **orally** and *within* **2 hours** *when given* **rectally.**
- ***Side effects***; *May cause* **abdominal cramping**, **electrolyte disturbances**, **melanosis coli** (pigmentation of the wall of the colon).

Senna alexandrina

- ***Pregnancy***; category **C.**
- ***Lactation***; *Not excreted in milk* (safe).
- ***Contraindications***; **intestinal obstruction**, **acute intestinal inflammation** (**Crohn's disease**), **ulcerative colitis**, **appendicitis**, and **abdominal pain** of ***unknown origin.***
- ***Other anthraquinone derivatives***; **Cascara** and **Aloe** (not used now).

Bisacodyl (Dulcolax®)

- **Bisacodyl** [bis-AK-oh-dil] is an ***organic compound*** of ***diphenylmethane derivatives.***
- **Bisacodyl** is ***widely used*** **stimulant laxative**.
- ***Uses***; - ***Short-term*** **relief of** ***acute or intermittent*** **constipation.**
  - ***Evacuation*** of the **bowel** *before* **surgery** or **colonic examinations.**
- ***Formulations***; **enteric-coated tablets** and **suppository.**
- ***Administration***; **orally**; ***once daily*** at **bedtime.**
- ***Onset***; **6-10 hours** *when given* **orally** and *within* **30-60 minutes** *when given* **rectally.**
- ***Pregnancy***; category **B.**
- ***Lactation***; *no data on the excretion into human milk* (safe).

Sodium Picosulfate (Picolax®) (Dulcolax® Pico)

- **Sodium Picosulfate** [pi-ko-SUL-fate] is a ***prodrug***, *metabolised by* **gut bacteria** into the **active compound**, this compound is a ***stimulant*** **laxative** and ***increases*** **peristalsis** in the gut.
- ***Uses***; - ***Short-term*** **relief of** ***acute or intermittent*** **constipation.**
  - ***Evacuation*** of the **bowel** *before* **surgery** or **colonic examinations.**
- ***Administration***; **orally solution** ***once daily*** at **bedtime.**
- ***Pregnancy***; category **B.** - ***Onset***; **6-12 hours.**

Castor Oil

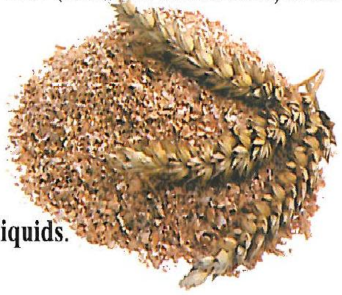
- **Castor Oil** is *obtained by* ***pressing*** the **seeds** of the **castor oil plant** (*Ricinus communis*).
- *Mechanism of action*; **Castor Oil** is ***broken down*** in the **small intestine** by **pancreatic lipase** to **ricinoleic acid**, which is ***very irritating*** to the **stomach** and **promptly** ***increases*** **peristalsis**.
- *Uses*; *reserved* for **total colonic evacuation**, *such as* **before** to ***surgery*** or ***radiologic*** or **endoscopy**.
- *Administration*; **orally, 16 hours** *before* **surgery** (*Onset*; **6-10 hours**).
- *Pregnancy*; ***should be avoid***, it may ***stimulate*** **uterine contractions**.

Bulk Forming Laxative

- **Bulk-forming laxatives** are ***indigestible***, ***hydrophilic*** **colloids** (indigestible parts of fruits & vegetables).
- They ***absorb*** **water**, ***forming*** a **bulky**, **emollient gel** in the **large intestine**, *causing* **water** ***retention*** and **intestinal** ***distension***, thereby ***increasing*** **peristaltic activity**.

Wheat Bran	**Wheat Dextrin** (Benefiber®)	**Methylcellulose** (Citrucel®)
Psyllium or Ispaghula (Meta-mucil®)	**Polycarbophil** (FiberCon®)	**Inulin** (Fiber Choice®)

- **Wheat Bran**; is an ***insoluble*** **fiber** ***extracted from*** **outer shell (bran)** of **wheat grain**.
- **Wheat Dextrin**; is a ***soluble*** **fiber** ***extracted from*** **wheat starch**.
- **Methylcellulose** is ***not absorbed***, is a ***hydrophilic colloid***.
- **Psyllium** [SILL-i-um] or **Ispaghula** [es-PAG-ula] is a form of fiber (***insoluble*** and ***soluble***) made from the ***husks*** of the *Plantago ovata* **plant's seeds**.
- **Polycarbophil** [POL-ee-KAR-boe-fil] is an ***insoluble*** **fiber**.
- **Inulin** [EN-ul-in] are a group of ***soluble*** *polysaccharide* **fibers** naturally occurring by many types of plants.



- *Site of action*; **small** and **large intestines**.
- *Onset of action*; **12-72 hours**.
- *Formulations*; ***soluble*** **fiber** can be ***incorporated into*** **foods** & **liquids**.
- *Uses*; ***Intermittent*** or ***chronic*** **constipation**.
- *Effectiveness*; - ***Least effective*** **laxatives**.
  - ***Requires*** **adequate water intake** to be ***effective***.
  - ***Less effective*** in **drug-induced constipation** and **slow-transit constipation** (STC).
- *Safety*; ***Safe*** in **renal** and **hepatic disease**, **pregnancy** and **geriatrics** (*old people*).
- *Side effects*; May cause gas and bloating.
- Agiolax® granules; **Seeds** of ***Plantago ovata***, **Ispaghula husk** and ***Senna*** **pods**.

Osmotic Laxatives

- **Osmotic laxatives**; are **substances** that ***increases*** **osmotic pressure**, *causing* **fluid** ***accumulation***, **colon** ***distension***, ***soft*** **stools**, and ***stimulates*** a **bowel movement**.

Glycerin

- **Glycerin** [GLIS-er-in] is *usually* **administered** as ***suppository*** and ***exerts*** its ***effect*** by ***irritating*** the **lining** of the **intestine** and **osmotic action** in the **rectum**.
- *Onset of action*; *within* **30 minutes**.
- *Uses*; ***acute*** or ***intermittent*** **constipation**.
- **Glycerin** is considered a ***safe laxative***, can be used in **pediatric patients**.

Lactulose (Duphalac®)

- **Lactulose** [LAK-too-lose] is a ***non-absorbable*** **disaccharide** (**Galactose** and **Fructose**) that is **used** ***orally*** or ***rectally*** in **constipation** and **hepatic encephalopathy** (reduce ammonia levels).
- *Mechanism*; **Lactulose** is ***metabolized by*** **colonic bacteria** to low-molecular-weight acids (**Lactic**, **Formic** and **Acetic**) resulting in an **osmotic effect** & ***lowers*** the **pH** and ***increases*** **colonic** ***peristalsis***.
- **Lactulose** is considered a ***safe laxative***, can be used in **pregnancy**.
- *Onset of action*; **1-2 days** (may require multiple doses).
- *Uses*; - ***Intermittent*** and ***chronic*** **constipation** (*including*; **chronic idiopathic constipation**; **CIC**), ***preferred*** in **chronic liver disease**.
  - It ***may*** use for ***acute*** **constipation** or in ***patients*** with an ***inadequate*** **response** to ***increased*** **dietary fiber** and **bulking agents**.
- *Side effects*; **nausea** and **abdominal discomfort** (**gas** or **bloating**).

Sorbitol

- **Sorbitol** [SOR-bi-tole] is a ***non-absorbable*** **sugar alcohol (monosaccharide)**, also exerts its effect by **osmotic action** same as **Lactulose** but ***less commonly*** used *than* **Lactulose**.

Polyethylene Glycol (PEG) (Miralax®)

- **Polyethylene Glycol 3350** [pol-ee-ETH-il-een-GLYE-kol] ***powder*** *for* **solution** is available as **laxative** and has been shown to cause ***less*** **cramping** and **gas** *than* ***other*** **laxatives**.

Saline Osmotic Laxatives

- **Saline osmotic laxatives** or **saline cathartics** are ***non-absorbable*** **salts**, which produce their effects primarily by **osmotic action**, *causing* **fluid *accumulation***, **colon *distension*** and ***stimulates*** a **bowel movement.**

Sodium Phosphate	**Magnesium Citrate**
Magnesium Hydroxide	**Magnesium Sulfate**

- ***Onset of action***; 0.5-3 hours (oral), 2-15 minutes (rectal).
- ***Uses***; **Acute constipation**, ***preoperative*** or ***pre-procedure*** **bowel preparation.**
- ***Contraindications***; **renal impairment, heart failure** and **cirrhosis.**
- ***FDA warning***; **patients** who ***received oral*** **Sodium Phosphate** for **bowel preparations** to **colonoscopy** *can development* of ***acute*** **phosphate nephropathy.**
- **Magnesium hydroxide** ***provides additional*** **bulk** and **stimulates *increased*** **contractions.**

Stool Softeners (Emollient Laxatives or Surfactants)

- **Stool Softeners** (**Emollient Laxatives** or **Surfactants**) are ***anionic surfactants*** that become ***emulsified*** with the **stool** *produce* ***softer*** **feces** and ***ease*** **passage.**

Docusate (Colace®)

- **Docusate** [DOK-yoo-sate] or **Dioctyl Sodium Sulfosuccinate** is a ***stool softener***. It works by helping **fat** and **water** *into the* **stool mass** to ***soften*** the **stool** (***emulsified*** **stool**).
- **Docusate** ***typically*** comes in the form of a **Sodium**, **Calcium** or **Potassium *salts***.
- ***Onset of action***; 1-3 days (oral), 5-20 minutes (rectal).
- ***Uses***; ***prophylaxis*** *rather than* **acute treatment**; ***Prevention*** of **opioid-induced constipation** (in combination with **Senna**) or ***prevention*** of **straining** in **post-myocardial infarction, postsurgical,** and **pregnant patients.**
- **Stool softeners *requires*** **adequate water *intake*** to be **effective.**
- **Stool softeners *should not*** be **taken *concomitantly with*** **Mineral Oil** *because* of the ***potential for absorption*** of the **Mineral Oil.**

Lubricant Laxatives

- **Lubricant laxatives** are ***substances*** that ***coat*** the **stool** and ***facilitating*** the **passage** of **hard stools.**

Mineral Oil

- **Mineral Oil** or **Paraffin Oil** is a ***clear***, ***viscous oil*** *derivative* of **petroleum** that ***lubricates*** **faecal material,** ***retarding*** **water absorption** *from* the **stool.**
- **Mineral Oil** may be ***given*** **orally** or **rectally.**
- ***Warning***; **Mineral Oil** *should be* ***taken*** **orally** in an **upright position** to ***avoid*** its **aspiration** and ***potential for*** **severe lipid pneumonitis.**
- ***Long-term*** **use** can *impair* **absorption** of **fat-soluble vitamins** (A, D, E, K).

Laxative Abuse

- Some of the ***less significant*** **adverse effects** of **laxative abuse** include; **dehydration, hypotension, tachycardia, postural dizziness** and **syncope.**
- **Laxative abuse** *can lead* to ***potentially fatal*** **acid-base** and **electrolyte imbalances.**

Chloride Channel Activators

- *Activation* of **chloride channels** in the **intestine** → *increase* **fluid secretion** in the ***intestinal lumen***.

Lubiprostone (Amitiza®)

- **Lubiprostone** [LOO-bi-PROS-tone] is the ***only agent*** in this class "***Chloride Channel Activator***", it is a ***bicyclic fatty*** acid ***derived from*** **Prostaglandin E_1**.
- *Mechanism*; *Act by* ***stimulating*** the **type 2 chloride channel** (ClC-2) in the ***small intestine***. This ***increases*** **chloride-rich fluid** ***secretion*** into the **intestine**, which ***stimulates*** **intestinal motility** and ***shortens*** **intestinal transit time**.
- *Advantages* ***over than other laxatives***; **not** or *little* ***cause***; **tolerance**, **dependency** or **electrolyte imbalance**.
- *Onset of action*; ***within*** **24-48 hours**.
- *Uses*; - **Chronic Idiopathic Constipation** (**CIC**).
  - **Irritable Bowel Syndrome** *with* **Constipation** (**IBS-C**) in **women** ≥ 18 years.
  - **Opioid-Induced Constipation** (**OIC**).
- *Most common side effects*; **nausea**, **diarrhea**, **headache** and **abdominal pain**.

Opioid Receptor Antagonists

- ***Acute*** and ***chronic*** **therapy** with **opioids** may *cause* **constipation** by ***decreasing*** **intestinal motility**, which ***results*** in ***prolonged*** **transit time** and ***increased*** **absorption** of **faecal water**.
- *Mechanism*; **opioid receptor antagonists** ***blocks*** **peripherally opioid receptors**, ***reverse*** **some** of the **side effects** of **opioid drugs** such as **constipation** ***without affecting*** **analgesia** or **withdrawals**.

Methylnaltrexone (Relistor®)

- **Methylnaltrexone** [METH-il-nal-TREX-one] (**MNTX**) is ***peripherally-acting µ-opioid antagonists***.
- *Mechanism*; ***blocks*** **peripherally opioid receptors**, ***reverse*** **some** of the **side effects** of **opioid drugs** such as **constipation** ***without affecting*** **analgesia** or **withdrawals**.
- *Uses*; **Opioid-Induced Constipation** (**OIC**).
- *Dose*; 0.15 mg/kg SC every 2 days.

Naloxegol (Movantik®)

- **Naloxegol** [nal-OX-ee-gol] is a ***peripherally-selective µ-opioid antagonist*** approved in 2014.
- *Uses*; **Opioid-Induced Constipation** (**OIC**); with ***chronic non-cancer*** **pain**.
- *Dose*; **25 mg** ***orally*** **once a day**; dose may be *reduced* to **12.5 mg** ***orally*** **once a day** for patients ***unable*** to **tolerate higher dose** (Adjust dose for CrCl <60 mL/minute).
- *Contraindications*; **patients** *with* **obstruction** ***use strong*** **CYP3A4 inhibitors**.

Alvimopan (Entereg®)

- **Alvimopan** [AL-vi-MOE-pan] are ***peripherally-acting µ-opioid antagonists***.
- *Uses*; **Postoperative ileus**.
- *Dose*; 12 mg orally within 5 hours before surgery and 12 mg twice daily after surgery until bowel function has recovered, but for ***no more*** than 7 days (*due to* ***possible*** **cardiovascular toxicity**).
- *N.B.*; **Naldemedine** is another peripherally-selective µ-opioid receptor antagonist under development in phase III clinical trials in the United States and Japan.

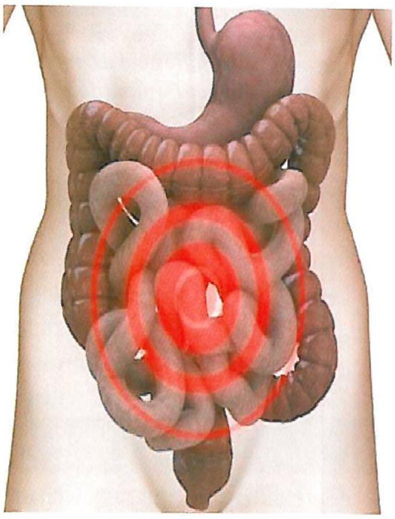
Guanylate Cyclase-C Agonists

Linaclotide (Linzess®)

- **Linaclotide** [lin-AK-loe-tide] is a ***Guanylate cyclase-C agonist***, approved in 2012.
- *Mechanism*; ***stimulates*** **secretion** of **chloride** and **bicarbonate** into **intestinal lumen**, which ***increases*** **intestinal fluid** and ***accelerates*** **intestinal transit**.
- *Uses*; - **Chronic Idiopathic Constipation** (**CIC**).
  - **Irritable Bowel Syndrome** *with* **Constipation** (**IBS-C**).
- *Dose*; **290 mcg** for **IBS-C** and **145 mcg** for **CIC**; ***orally*** **once daily** on an ***empty*** **stomach**, at *least* **30 minutes** *prior* to **first meal** of the **day**.
- *Warning*; ***Contraindicated*** in **infants** and **children** < 6 years of age. ***Avoid*** use in **children** and **adolescents** 6–17 years of age.

Irritable Bowel Syndrome (IBS)

Overview:-



- **Irritable Bowel Syndrome** (**IBS**) is a ***common***, ***long-term*** **condition** (*often years*) that *affects* the **large intestine (colon).**
- **IBS** ***commonly*** *causes* **cramping, abdominal pain, bloating, gas, diarrhea** and/or **constipation.**
- *About* **9-23%** of **people** in the ***developed world*** are *believed to* be affected by **IBS** (WHO 2009).
- **IBS** is ***more common*** in **women**, and **patients** *younger than* **50 years.**
- **IBS** *affects* **quality of life** and *may* result in ***missed*** **school** or **work.**
- **Disorders** such as **anxiety, major depression,** and **chronic fatigue syndrome,** are *common* among *people with* **IBS.**
- **IBS**; *unlike* **ulcerative colitis** and **Crohn's disease,** which are forms of **inflammatory bowel disease, IBS** ***doesn't cause*** **changes** in **bowel tissue** or ***increase*** **risk** of **colorectal cancer.**

Definitions:-

- **Irritable Bowel Syndrome** (**IBS**); is a **functional** (*not* structure) **GI disorder** ***characterized by*** **abdominal pain** and **altered bowel habits** in the ***absence*** of a **specific** and **unique** ***organic pathology.***
- **IBS** ***divides into*** the *following subtypes*;
  - **Diarrhea** *predominant* (**IBS-D**).
  - **Constipation** *predominant* (**IBS-C**).
  - **Mixed IBS** (**IBS-M**) or **Alternating IBS** (**IBS-A**); *features* of ***both*** **IBS-D** and **IBS-C.**
  - **Unclassified** (**IBS-U**).
- *N.B.*; **Post-Infective syndrome** has consequently been ***termed*** **"Post-Infectious IBS"** (**IBS-PI**).

Symptoms:-

- ***In addition*** to **diarrhea** and/or **constipation, abdominal pain** is often a **component** of ***all subtypes.***
- ***Other symptoms***; **bloating, distension, spasm** and **urgency.**

Pathophysiology:-

- **IBS pathophysiology** of is ***not clear.***
- ***Many theories*** have been ***put forward***, but the ***exact*** **cause** of **IBS** is ***still uncertain.***
  - **Alterations in GI motility**; *Alteration* in **frequency** & **irregularity** of **luminal contractions.**
  - **Visceral hypersensitivity**; ***increased*** **sensation** in ***response to*** **stimuli.**
  - **Brain-gut axis**; *alterations* in ***communications*** between the **enteric nervous system** & **CNS.**
  - **Post-infectious**; *about* **10%** of **IBS** cases are ***triggered by*** an **acute gastroenteritis infection.**
  - **Genetics.**

Diagnosis:-

- **Patient's pattern** of **symptoms** may ***provide*** insight *into* **subtype.**
- ***Several*** **diagnostic criteria** have been ***developed***;
  - **Rome III criteria** (*most common*);
    - ***Recurrent*** **abdominal pain** or **discomfort** ***at least*** **3 days/month** in the ***last*** **3 months** ***associated with*** **two** or **more** of the *following*;
      - * ***Improvement*** *with* **defecation.**
      - * **Onset** *associated with* a ***change*** in **frequency** of **stool.**
      - * **Onset** *associated with* a ***change*** in **form** (appearance) of **stool.**
    - **Symptoms** ***should have*** **started** ***at least*** **6 months** *before* **diagnosis.**

- **Manning criteria**;
  - *At least* **2** of the *following*:
    - * *Onset* of **pain** *linked to more* **frequent bowel movements**.
    - * **Looser stools** *associated with* ***onset*** of **pain**.
    - * **Pain** *relieved by* **passage** of **stool**.
    - * ***Noticeable*** **abdominal bloating**.
    - * ***Sensation*** of ***incomplete*** **evacuation** *more than* **25%** of the time.
    - * **Diarrhea** *with* **mucus** *more than* **25%** of the time.
- **American College of Gastroenterology** (**ACG**) **guidelines** ***also*** **recommend**;
  - *Screening for* **celiac disease** in *patients* with **IBS-D** and **IBS-M**.
  - *No* **endoscopy** if *younger than* **50 years** and ***no alarm*** **symptoms**.
  - *No* **routine food allergy** ***testing***.
  - *No* **routine** ***checking for*** **small intestinal bacterial** ***overgrowth unless*** **lactose intolerance** is a **concern**, ***despite*** **dietary intervention**.
- **Guidelines recommend**;
  - If ***other*** **GI diseases** are **excluded** and ***no alarm*** **features** (e.g., **weight loss**, **bleeding** and **anemia**) are **present**, ***diagnosis*** of **IBS** ***can*** be **made** ***with*** **confidence**.

➤ Treatment Strategies:-

- **Treatment** *involves* a *mix of* **drug**, **diet**, and **psychosocial interventions**.
- **Cognitive behavioral therapy**, **dynamic psychotherapy** and **hypnotherapy** have ***all shown effectiveness*** in **IBS**.

A) **Dietary Modifications**;

- *Avoid* **foods *that* trigger symptoms** (*such* as gases forming foods as lentils, legumes & beans).
- *Low* **FODMAP diet** (Fermentable, Oligo-, Di-, Mono-saccharides And Polyols); are *short chain* **carbohydrates** that are ***poorly*** **absorbed** in the **small intestine**. They include ***short chain*** **oligo-saccharide** polymers of fructose (fructans) and galactooligosaccharides (GOS, stachyose, raffinose), disaccharides (lactose), monosaccharides (fructose), and sugar alcohols (polyols), such as sorbitol, mannitol, xylitol and maltitol.
- **Fiber supplementation**; may ***improve*** **symptoms** of **constipation** and **diarrhea**.

B) **Pharmacological Therapies**;

Antispasmodics

- ***Antispasmodics***: Used mostly for ***short-term relief*** of **abdominal pain *but may also treat* diarrhea** in *patients with* **IBS-D**.

Dicyclomine or **Dicycloverine** (Bentyl®)	**Hyoscine N-Butylbromide** (Buscopan®)
Clidinium (Librax®)	**Peppermint Oil**

- **Dicyclomine** or **Dicycloverine** ***used*** to **reduce** the **abdominal pain** in **irritable bowel syndrome (IBS)**, ***side effects***; **anticholinergic side effects**.
- **Hyoscine butylbromide** ***most popular antispasmodic drug***, ***side effects***; **anticholinergic side effects**.
- Librax®; **Clidinium** + **Chlordiazepoxide** (*benzodiazepine derivative;* **Anxiolytics**); ***used*** for ***short-term relief*** to **reduce** the **abdominal pain** in **irritable bowel syndrome (IBS)** (in some patient if comorbid anxiety exists); ***Long-term*** **use** may cause **dependence** and **tolerance**. ***Side effects***; **anticholinergic side effects**. **Warnings**; Concomitant use of **benzodiazepines** (including Librax®) and **opioids** may result in **sedation**, **respiratory depression**, **coma** and **death**.
- **Peppermint oil**; may ***worsen*** **GERD** but may ***improve*** **symptoms** in **IBS**.

Mebeverine (Duspatalin®)

- **Mebeverine** is an ***antispasmodic drug without*** **anticholinergic** ***side-effects*** (this relieves painful muscle spasms of the gut, without affecting its normal motility).
- It ***used*** to **reduce** the **abdominal pain** in **irritable bowel syndrome (IBS)**.

Pinaverium (Spasmopinaver®)

- **Pinaverium** is an ***antispasmodic drug*** acts as a **calcium channel blocker**.

Tricyclic Antidepressants

- *Tricyclic Antidepressant*; Used to ***relief*** **pain**, ***improve*** **global symptoms**, and ***slow*** **motility** in *patient with* **IBS-D**, ***but can*** be used in **IBS-C** ***but*** may ***worsen*** **constipation**, ***especially*** *if* **comorbid depression** or **anxiety exists**.

Imipramine (Tofranil®) | **Amitriptyline** (Tryptizol®) | **Nortriptyline** (Pamelor®)

- **Imipramine**, **Amitriptyline** and **Nortriptyline** are the ***most studied***.
- *Actions in IBS*; at **doses** ***sub-therapeutic*** for **antidepressive actions**.
    - ***Increases*** **pain threshold** in the **gut** (providing a visceral analgesic effect).
    - ***Delayed*** **gastric emptying** and ***decrease*** **stool frequency**.
- *Precautions*; *Potential for* **anticholinergic effects**, **sedation**, **CV effects**, and **drug interactions**.

Selective Serotonin Reuptake Inhibitors (SSRIs)

- *Selective Serotonin Reuptake Inhibitors (SSRIs)*; Used to ***relief*** **pain**, ***improve*** **global symptoms**, ***similar to*** *Tricyclic Antidepressant*. *Used for both* **IBS-D** and **IBS-C**.

Fluoxetine (Prozac®) | **Sertraline** (Lustral®) | **Paroxetine** (Seroxat®)

Citalopram (Cipram®) | **Escitalopram** (Cipralex®)

- **Fluoxetine**, **Sertraline**, **Paroxetine**, **Citalopram** and **Escitalopram** are *all* ***viable*** **options**.

Probiotics

- ***Some*** evidence to ***support*** **probiotics** in ***improvement*** in **global symptoms**, **bloating** and **flatulence**.

Drugs for IBS-C

Laxatives

- **Laxatives** *was* **discussed** in the ***previous topic***.
- **Psyllium** has ***best evidence***; however, it may cause **bloating** and **gas formation**.
- **Calcium Polycarbophil** may be ***used as*** an ***alternative*** **bulk-forming agent** (**wheat** or **corn bran** ***should not be*** **used**).
- **PEG**-***based*** **laxatives** may ***increase*** *stool frequency*, but they have ***no effects*** on ***reductions*** in **abdominal pain** in IBS (*minimal to no bloating*).
- ***Avoid*** **stimulant laxatives** because they may ***worsen*** **abdominal pain**.

Chloride Channel Activators

Lubiprostone (Amitiza®)

- **Lubiprostone** *was* **discussed** in the ***previous topic***.
- **Lubiprostone** [LOO-bi-PROS-tone] it is a ***derived from*** **Prostaglandin E_1**.
- ***Used*** in **Irritable Bowel Syndrome** *with* **Constipation** (**IBS-C**) in **women** ≥18 years.
- ***Most common side effects***; **nausea**, **diarrhea**, **headache** and **abdominal pain**.

Serotonin Agonists

Tegaserod (Zelmac®)

- **Tegaserod** [teg-a-SER-od] is a **5-HT$_4$ partial agonist** in the **enteric nervous system** (**ENS**) in the **GIT**, which ***stimulates*** **GI motility**. ***Used*** for **IBS-C**.
- ***Efficacy***; ***Improves*** **pain**, **global symptoms**, and **motility**.
- It is ***removed*** from the market in 2007 due to FDA concerns about possible ***increased risks*** of **heart attack** or **stroke** (In **US** **Tegaserod** is ***available only*** on an **emergency-use**).

Mosapride (Fluxopride®)

- **Mosapride** [Moos-a-pride] is a **5-HT$_4$ partial agonist** and ***indirectly*** as a **parasympathomimetic** (***increase*** **ACh release**); ***gastroprokinetic agent***.
- It is ***used*** for the treatment of **irritable bowel syndrome** with **constipation** (**IBS-C**).
- It is available in some countries (e.g. Egypt), ***Now*** no data available to insure QT prolongation.
- ***Drug interaction***: **LMEIs** (e.g. **Erythromycin**) ***may cause*** ⇨ **QT interval** ***prolongation***.

Guanylate Cyclase-C Agonists

Linaclotide (Linzess®)

- **Linaclotide** *was* **discussed** in the ***previous topic***.
- **Linaclotide** is a ***Guanylate cyclase-C agonist***, approved in 2012.
- ***Used*** in **Irritable Bowel Syndrome** *with* **Constipation** (**IBS-C**); **290 mcg *orally* once daily** on an ***empty* stomach**, at *least* **30 minutes** *prior* to **first meal** of the **day**.
- ***Warning***; ***Contraindicated*** in **infants** and **children** < 6 years of age. ***Avoid*** use in **children** and **adolescents** 6–17 years of age.

Drugs for IBS-D

Antibiotics

- A ***short course*** (10–14 days) of **non-absorbable antibiotic** (**Rifaximin**) may ***improve*** **global symptoms** of **IBS**, ***especially*** **bloating** in **IBS-D**.

Antimotility Agents

- **Antimotility Agents** *was* **discussed** in the ***previous topic***.

Loperamide (Imodium®) | **Diphenoxylate/Atropine** (Lomotil®)

- **Loperamide** and **Diphenoxylate** is an **opioid drug**, act as **μ receptor *agonist***.
- ***Efficacy***; ***reduces*** **motility** and ***increases*** **stool consistency** (***no*** **effects** on **global symptoms** or **pain** ***but reduces*** **motility** and ***increases*** **stool consistency**).
- May be used as an ***adjunct*** to **other therapies** in **IBS-D**.
- ***Contraindications***; ***high* fever**, ***bloody*** or ***black*** **stool** and in **children > 2 years**.

Serotonin Antagonists

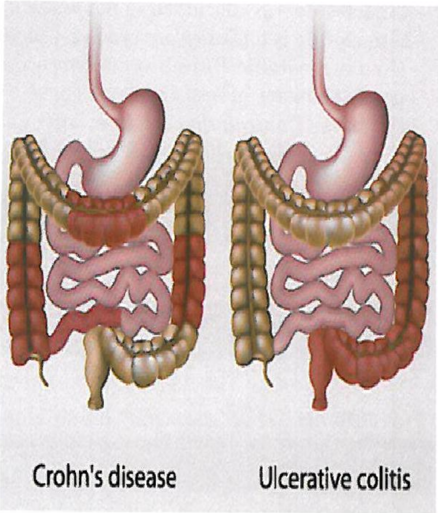
Alosetron (Lotronex®) | **Cilansetron** (Calmactin®)

- **Alosetron** [a-LO-ze-tron] and **Cilansetron** [see-LAN-ze-tron] are **$5\text{-}HT_3$ receptor antagonist** ***used*** for the management of severe **irritable bowel syndrome** with **diarrhea** (**IBS-D**).
- **Alosetron *used only*** in **women**, ***but*** **Cilansetron** effective in **men** as well as **women**.
- ***Side effects***;
  - **Alosetron**; ***serious*** (***life-threatening***) **complications** of **constipation** e.g. **ischemic colitis** *may lead to* **obstruction**, (**Alosetron** was ***withdrawn*** from market, ***but*** it is become ***available*** **again**).
  - **Cilansetron** is **constipation**, ***less*** or ***self-limited*** **serious complications**.

- *N.B.*; **Sulpiride** (Dogmati®) is an ***atypical antipsychotic*** some physicians can prescribe it for ***some*** IBS patients; relief abdominal pain, anxiety, depression and correct stool.

Inflammatory Bowel Disease (IBD)

➢ Overview:-



- **Inflammatory Bowel Disease (IBD)**; is a ***group of* inflammatory conditions** of the **colon** and **small intestine**.
- ***Two major types*** of **inflammatory bowel disease** are **ulcerative colitis (UC)** and **Crohn's disease (CD)**.
- **Ulcerative colitis (UC)**, which is ***limited to*** the **colon** and **rectum**.
- **Crohn disease (CD)**; which can ***affect any*** **segment** of the **GIT** from the **mouth** to the **anus**.
- **Inflammatory Bowel Disease (IBD)** ***fall into*** the **class** of **autoimmune diseases**, it is *thought* that the **inflammation** is ***secondary to*** **immune system** ***attacks***.
- *Approximately* **1-1.3 million** people in the **United States**.

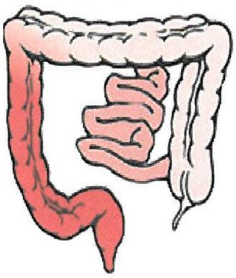
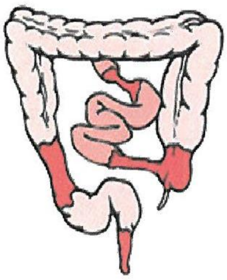
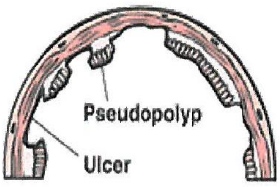
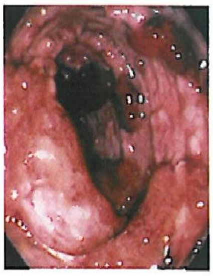
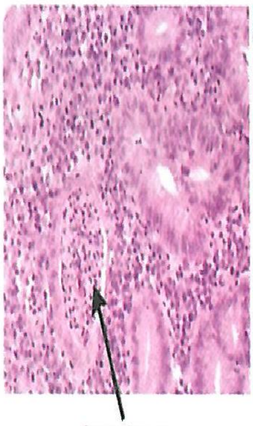
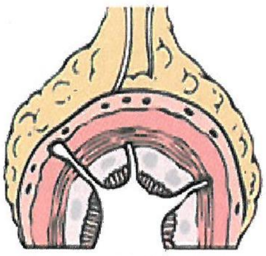
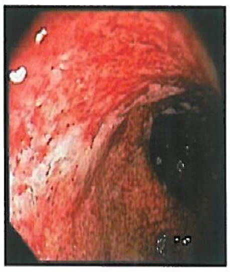
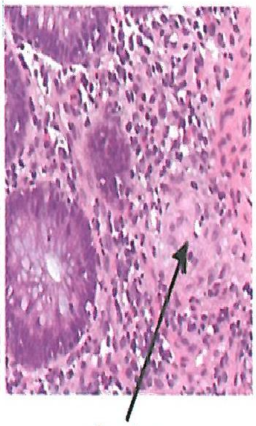
➢ Pathophysiology:-

- The ***exact cause*** is ***unknown***.
- ***Contributing factors***;
  1) ***Dysregulated*** **immune response**.
  2) **Genetics**; ***first-degree relatives*** of **affected patients** have a **4–20 times** ***higher*** **risk** of *developing* **IBD**.
  3) **Environmental**;
     - **Diet**; **Trigger foods** (*dietary antigens*) may also *contribute* to **ongoing inflammation**.
     - **Luminal bacteria**; ***Endogenous*** **intestinal bacteria** *may* **contribute** to **IBD**.
     - **NSAIDs**; ***Worsen*** **IBD**, ***lead to*** **disease flares** (inhibition of COX may impair mucosal barrier protective mechanisms).
     - **Smoking**; ***Worsens*** **CD**; however, is associated with ***improvement*** in **UC symptoms**.
  4) **Proinflammatory cytokines**; **Interleukin-1 (IL-1)**, **interleukin-6 (IL-6)**, and **tumor necrosis factor (TNF)**, ***release*** and ***contribute to*** the **ongoing inflammatory**.

➢ Symptoms:-

- **Symptoms** *may vary* ***depending on*** **disease location**.
- ***Common*** **symptoms** in **both diseases** (**UC** and **CD**) *include*;
  - **Fever**.
  - **Abdominal pain**.
  - **Diarrhea** (*may be* **bloody**, **watery** or **mucopurulent**).
  - **Rectal bleeding**.
  - **Weight loss**.
- ***Common*** **complications**;
  - **Perianal disease** (**anal fissures**, **fistulas** and **abscesses**): **50%** of ***patients with*** **CD**.
  - **Colon cancer** (***Common*** in **UC**).
- ***Extra-intestinal*** **symptoms** (10-20%);
  - **Hepatobiliary Complications**;
    - **Hepatic** ***complications***; fatty liver, pericholangitis, chronic active hepatitis, and cirrhosis.
    - **Biliary** ***complications***; primary sclerosing cholangitis, cholangiocarcinoma, and gallstones.
  - **Joint Complications**; arthritis (asymmetric), sacroiliitis and ankylosing spondylitis.
  - **Ocular Complications**; iritis, uveitis, episcleritis and conjunctivitis.
  - **Dermatologic Complications**; erythema nodosum, pyoderma gangrenosum and aphthous ulceration.

Clinical Features:-

Clinical Findings	Ulcerative Colitis (UC)	Crohn Disease (CD)
Bowel involvement	- Rectum and colon	- *Commonly in* ileum
Perianal involvement	- Rare	- Common
Depth of ulceration	- Superficial	- May extend to submucosa or deeper
Distribution of disease	- Continuous area of inflammation 	- Patchy areas of inflammation 
Histology	- Nontransmural - Pseudopolyps  Pseudopolyp Ulcer  - Crypt abscesses  Crypt abscess	- Transmural lesions - Cobblestone  Transmural inflammation Ulcerations Fissures  - Granulomas 
Risk for toxic megacolon	- Common	- Rare
Malabsorption	- Rare	- Common
Risk for colorectal cancer	- Common	- Uncommon

➢ Severity of Ulcerative Colitis:-

Mild	- <4 stools/day (±blood). - No fever, anemia or tachycardia. - Normal ESR.
Moderate	- >4 stools/day (±blood) - Minimal signs of systemic toxicity.
Severe	- >6 stools/day with blood - Temp >99.5°F (37.5°C) - HR >90 beats/minute - ESR >30 mm/hour - Hb <75% of normal - Abdominal tenderness - Bowel wall edema
Fulminant	- >10 stools/day with continuous blood - Temp >99.5°F (37.5°C) - HR >90 beats/minute - ESR >30 mm/hour - Transfusions required - Abdominal pain - Dilated colon

R; Truelove and Witt criteria

➢ Severity of Crohn Disease:-

Mild - Moderate	- Absence of fever - Dehydration - Abdominal tenderness - < 10% weight loss
Moderate - Severe	- Anemia - Nausea and vomiting - Severe weight loss
Severe - Fulminant	- High temperature. - Abdominal pain. - Persistent vomiting. - Abscess.

➢ Diagnosis:-

- **Patient Examinations**; *may include*;
  - **Fever**, **tachycardia**, **dehydration**, **toxicity**, **pallor** and **anemia**.
  - **Toxic megacolon**; May be present in UC.
  - **Perianal complications**: May be observed in up to 90% of cases of CD.
- **Endoscopic Examinations**.
- **Imaging Examinations**.

➢ Management:-

- **Goals**;
  - *Achievement* of **remission** (**induction**); relieve active symptoms.
  - *Prevention* of **disease flares** (**maintenance**); prevent recurrence.
- The **care** of a **patient** *with* **IBD** can be *either* **medical** or **surgical** or, in many patients, a ***combination*** of **both**.
- **Antimotility** (**Loperamide**) and **Antispasmodics** can be used to ***control*** **symptoms**.
- **Treatment** is ***selected on*** the **basis** of **disease location** and **severity**.

➢ Medications Used to Treat IBD:-

Aminosalicylates

- Aminosalicylates was the *first agents* used to **treat IBD**.
- Aminosalicylates are drugs that ***contain*** **5-aminosalicylic acid** (**5-ASA**).
- **5-ASA** ***differs from*** Salicylic Acid ***only*** by the ***addition*** of an **amino group** at the **5** (*meta*) **position**.
- Used for ***both***;
    1) *Induction* of **remission** (relieve symptoms and inflammation).
    2) *Maintenance* of **remission** (prevent the disease from becoming active again).
- Aminosalicylates are ***believed*** to **work** ***topically*** (not systemically).

Azo Compounds

Sulfasalazine (Azulfidine®)	**Balsalazide** (Colazal®)	**Olsalazine** (Dipentum®)

- **Azo compounds** ***contain*** **5-ASA** *bound by* an **azo** (N=N) **bond** to ***another*** **compound** to ***reduces absorption*** of the **5-ASA** *from the* **small intestine**, **colonic bacteria** ***cleave*** the **azo bond** and ***releasing*** the ***active*** **5-ASA**.
- **Sulfasalazine** [SUL-fa-SAL-a-zeen] is a ***prototype agent***, *cleaved by* **colonic bacteria** to the **active portion** (**5-ASA**) and the ***inactive*** **carrier** molecule **Sulfapyridine**.
- **Balsalazide** [bal-SAL-a-zide] and **Olsalazine** [ol-SAL-a-zeen] are ***non- sulfa azo compounds***.
- *Efficacy*; ***best*** in **colonic disease** (because of the colonic activation of the drug).
- *Mechanism of action*; ***Inhibits*** **prostaglandin** and **leukotriene synthesis** (*local* anti-inflammatory).

Dose	**Sulfasalazine**	; 4–6 g/day for induction and 2–4 g/day for maintenance.
	Olsalazine	; 1–3 g/day.
	Balsalazide	; 2–6.75 g/day.

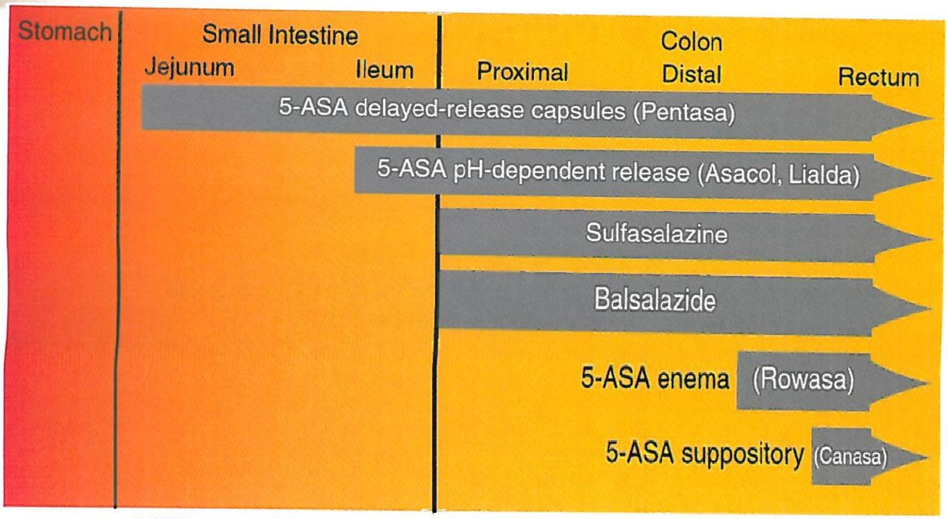
- *Side Effects* (dose-related); GI disturbance, headache, arthralgia and folate malabsorption.
- *Idiosyncratic side effects*: rash, fever, pneumonitis, hepatotoxicity, bone marrow suppression, hemolytic anemia, pancreatitis and decreased sperm production in men.
- *Contraindications*; **Sulfasalazine** is ***avoid*** in *patients with* a **sulfa allergy**.
- *Monitoring/Follow-Up*;
    1) **Patients** ***should be*** *given* **folate supplements**.
    2) **Renal function** ***should be*** *monitored* in patients with ***pre-existing*** **renal failure**.
    3) **CBC** & **creatinine level** *every* **3-6 months** of **therapy**.

Mesalamine Compounds

Mesalamine (Pentasa®) (Rowasa®) (Canasa®) (Delzicol®) (Asacol® HD) (Lialda®) (Apriso®)

- **Mesalamine** [me-SAL-a-meen] is ***designed to*** *deliver* **5-ASA** to ***different*** **segments** of the **small** or **large intestine**.
- *In general*; ***better*** **tolerated** than **Sulfasalazine**; *considered* ***first line*** in **mild–moderate UC & CD**.
- *Formulations*; **Product** ***selection*** *depends on* **location** of **disease**.

Product	Formulation	Daily Dosage (g)	Site of Action
Pentasa®	Timed-release microgranules	2-4	- Small intestine - Colon
Delzicol®	Delayed-release capsules	1.6-4.8	- Distal ileum - Colon
Asacol®	Delayed-release resin (dissolves at pH >6-7)		
Apriso®	Enteric-coated granules in a delayed-release polymer matrix (dissolves at pH >6-7)	0.375-1.5 once	- Colon
Lialda®	Delayed-release Multi Matrix (MMX) System tablet (dissolves at pH >6-7)	2.4-4.8 once	- Colon
Canasa®	Suppository	1	- Rectum
Rowasa®	Enema	4	- Rectum - Terminal colon


Stomach
Small Intestine
Jejunum
Ileum
Colon
Proximal
Distal
Rectum
5-ASA delayed-release capsules (Pentasa)
5-ASA pH-dependent release (Asacol, Lialda)
Sulfasalazine
Balsalazide
5-ASA enema (Rowasa)
5-ASA suppository (Canasa)

5-ASA *release from* **different formulations** in the **small** and **large intestines**

Antibiotics

Ciprofloxacin (Cipro®)	**Metronidazole** (Flagyl®)

- The **rationale** *behind* ***using*** **antibiotics** for **IBD patients** to help *re-establish* **balance** in the **gastrointestinal flora.**
- The ***most commonly*** used agents (alone or in combination) are:
    - **Metronidazole**; 500-750 mg orally 3 times daily.
    - **Ciprofloxacin**; 500-750 mg orally 2 times daily.
- ***Indications*** of **antibiotics** in **IBD**;
    - ***Adjunctive*** **treatment** *along with* ***other*** **medications** for **active CD.**
    - **Treatment** for ***complications*** in **CD** (e.g.; **fistulas, perianal disease**).
    - **Prophylaxis** of **CD** ***recurrence*** in **post-operative patients.**
- **Note**; that **antibiotics** ***do not*** have a **role** in the **management** of **UC.**

Glucocorticoids

Prednisone (Hostacortin®)	**Prednisolone** (Hostacortin-H®)	**Budesonide** (Entocort®)
Methylprednisolone (Depo-Medrol®)	**Hydrocortisone** (Solu-Cortef®)	

- **Corticosteroids** are *rapid-acting* **anti-inflammatory agents.**
- ***Efficacy***; are indicated ***only*** for **acute flares** (*no* role in the maintenance of remission).
- **Corticosteroids** are ***not useful*** for ***maintaining*** **disease remission.**
- ***More than*** **50%** of **patients** with **severe disease** may *become* **steroid-dependent.**
- ***Administration***; by ***various*** **routes** *depending on* the **location** and **severity** of **disease**;
    - **IV**; **Methylprednisolone** (15-48 mg/day) and **Hydrocortisone** (100 mg every 8 hours).
    - **Orally**; **Prednisone** (20–60 mg/day), **Prednisolone** (20–60 mg/day) and **Budesonide** (9 mg/day).
    - **Topically**; Enema, suppository or foam preparations.
- **Budesonide** is a ***potent*** **synthetic analog** of **Prednisolone**, but is subject to ***rapid*** **first-pass hepatic metabolism**, resulting in ***low*** **oral bioavailability.**
- ***Higher doses*** have ***not been*** **shown** to be **more efficacious** but have ***significantly*** **greater adverse effects.**
- ***Side effects***; **adrenal suppression, glucose intolerance, hypertension, sodium/water retention, osteoporosis, cataracts,** and **impaired wound healing.**

Immunomodulators

6-Mercaptopurine (6-MP) (Purinethol®) — Azathioprine (AZA) (Imuran®)

Methotrexate (MTX)

- **Immunomodulators** have a ***slower* onset of action** (at least 3 months); ***not used for*** **induction** of **remission.**
- *Efficacy*; Used for **maintenance of remission** in **patients** ***intolerant*** of or ***not responsive*** to **Aminosalicylates.**
- **Azathioprine** [AY-za-THYE-oh-preen] and **Mercaptopurine** [mer-KAP-toe-PURE-een] are **purine antimetabolites** that have **immunosuppressive properties.**
- **Methotrexate** [meth-oh-TREX-ate] is ***another*** **antimetabolite** that has beneficial effects in a number of **chronic inflammatory diseases** (**Crohn's disease** and **rheumatoid arthritis**) and in **cancer.**
- *Doses*;
    - **Azathioprine**; 2–2.5 mg/kg/day orally.
    - **Mercaptopurine**; 1–1.5 mg/kg/day orally.
    - **Methotrexate**; 15–25 mg/week intramuscularly (Crohn's disease only).
- *Side effects*; **Bone marrow suppression, anemia, nausea, diarrhea, rash** and **hepatotoxicity.**
- **Folate** ***supplementation*** *reduces* the **risk** of these events *without* **impairing** the **anti-inflammatory action.**

Biologic Agents

TNF-a Inhibitors

- **Tumor necrosis factor alpha** (**TNF-α**) is a ***pro-inflammatory cytokine.***
- There are ***currently* 5 TNF inhibitors**; **Etanercept**, **Infliximab**, **Adalimumab**, **Certolizumab** and **Golimumab.**

***Precautions*** or ***Contraindications***; for **anti-TNF agents**;

- ***Risk of*** **serious infections,** or ***history of*** **recurring infections; black box warning.**
- **Recent malignancies;** *especially* **lymphoproliferative cancer; black box warning.**
- **Congestive heart failure (CHF)**; New York Heart Association (NYHA) class III or IV heart failure
- **Demyelinating diseases;** *like* **multiple sclerosis.**
- ***Avoid*** **vaccination** *with* **live vaccines.**

Infliximab (Remicade®)

- **Infliximab** [in-FLIX-i-mab] is a ***recombinant*** **DNA-derived chimeric human-mouse** (75% human, 25% mouse) **IgG1 monoclonal antibody.**
- *Efficacy*; - **Maintenance of remission of moderate–severe CD** and **UC.**
    - **Perianal fistulizing CD.**
- *Dose*; IV Infusion, 5 mg/kg as single dose, followed by 5 mg/kg at 2 and 6 weeks, then every 8 weeks as maintenance. (Patients losing response with time may be treated with a 10-mg/kg dose).
- **Infusion site reactions** ***may*** **occur** and may ***correlate with*** **anti-infliximab antibodies** ***formation*** (antihistamines may prevents some of these reactions).

Adalimumab (Humira®)

- **Adalimumab** [a-dal-AYE-mu-mab] is a ***recombinant fully*** **human IgG1 monoclonal** ***antibody.***
- *Efficacy*; **Maintenance of remission of moderate–severe CD** and **UC,** in **patients** ***unresponsive*** to **conventional therapy**; also *indicated for* **patients** who **no longer** *respond to* **Infliximab.**
- *Dose*; Induction; 160 mg SC on day 1 (given as four separate 40-mg injections) or two 40-mg/day injections for 2 consecutive days, followed by 80 mg SC 2 weeks later (day 15). Then, can decrease dose to 40 mg SC every 2 weeks starting on day 29 of therapy.

Certolizumab Pegol (Cimzia®)

- **Certolizumab** [ser-toe-LIZ-oo-mab] is a ***unique*** **TNF-α blocker** that contains a ***recombinant, humanized*** **antibody Fab fragment** ***conjugated to*** a **Polyethylene Glycol (PEG)** (not contain **IgG_1**) with ***specificity*** for ***human*** **TNF-α**.
- *Efficacy*; **Maintenance of remission of moderate–severe CD**, in **patients** ***unresponsive*** to **conventional therapy**.
- *Dose*; 400 mg **SC** initially and repeat at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks.

Golimumab (Simponi®)

- **Golimumab** [goe-LIM-ue-mab] is a ***human*** **monoclonal antibody** with a ***high*** **affinity** for ***soluble*** and ***membrane-bound*** **TNF-α**.
- *Efficacy*; **Maintenance of remission of moderate–severe UC**, in **patients** ***unresponsive*** to in **previous therapies** or ***requiring*** *continuous* **steroid therapy**.
- *Dose*; 200 mg subcutaneously at week 0, then 100 mg at week 2, then 100 mg every 4 weeks.

Anti-integrin Agents

Natalizumab (Tysabri®)

- **Natalizumab** [NA-ta-LIZ-ue-mab] is a ***humanized*** **monoclonal antibody** ***against*** the **α-4 subunit of integrin molecules** (*leukocytes*), *used* in the **treatment of multiple sclerosis & Crohn's disease**.
- *Efficacy*; **Maintenance of remission of moderate–severe CD**, in **patients** ***unresponsive*** to **conventional therapies** and **TNFα** ***inhibitors***.
- *Dose*; 300 mg IV infusion over 1 hour every 4 weeks, the treatment cost is very expensive.
- *Precautions*; **Progressive Multifocal Leukoencephalopathy**; **PML** (viral CNS infection, John Cunningham virus; JCV); rapidly progressive and usually results in death or permanent disability. The ***risk of PML***; **1**) history of previous immunosuppression. **2**) Long duration of **Natalizumab** treatment, beyond 2 years. **3**) JC virus antibody positivity.

Vedolizumab (Entyvio®)

- **Vedolizumab** [VE-doe-LIZ-ue-mab] is a ***humanized*** **monoclonal antibody** ***against*** the **$\alpha 4\beta 7$-integrin of integrin molecules** (*leukocytes*).
- *Efficacy*; **Maintenance of remission of moderate–severe CD** and **UC** in **patients** ***unresponsive*** to **conventional therapies** and **TNFα** ***inhibitors***.
- *Dose*; 300 mg IV given at 0, 2, and 6 weeks, then given every 4 weeks. Discontinue if no evidence of improvement at 14 weeks.
- *Precautions*; similar to that of **Natalizumab**, ***but*** with ***lower risk*** of **PML**.

Novel Agents

Ustekinumab (Stelara)

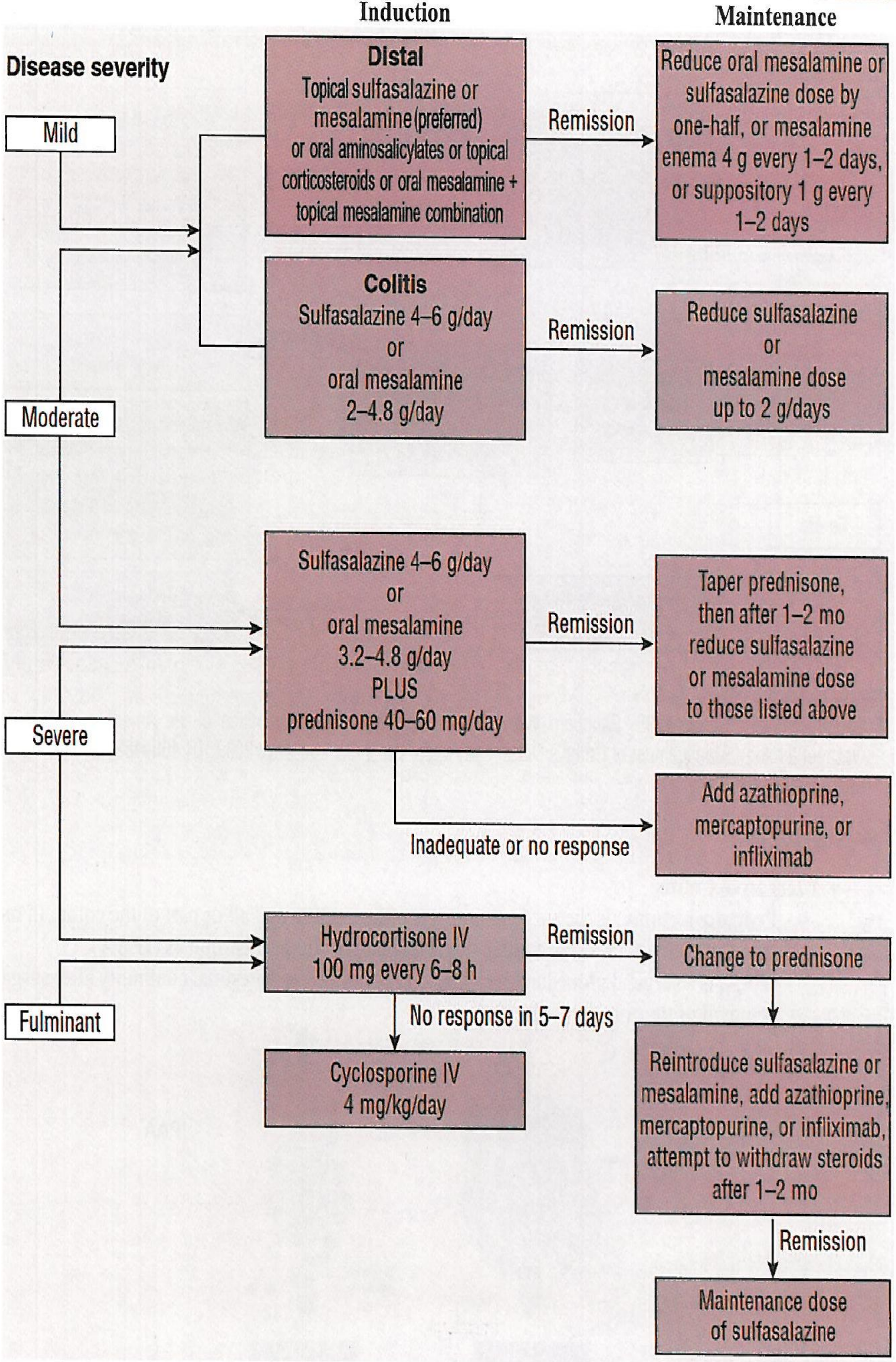
- **Ustekinumab** [YOO-sti-KIN-ue-mab] is a ***humanized*** **monoclonal antibody** ***against*** **interleukin 12** and **interleukin 23**.
- **Ustekinumab** is ***not approved*** yet.
- **In November 2016**; UNITI trial were published Ustekinumab use for both induction and maintenance of remission in patients with severe drug unresponsive Crohn's disease, results showed higher rates of response compared to placebo.

➢ **IBD during Pregnancy and Breastfeeding:-**

- **Aminosalicylates** (*except* Asacol® HD, has dibutyl phthalate "DBP" in the coating) and **Steroids** *may be* **administered** ***during*** **pregnancy** and **breastfeeding** with the ***same*** **guidelines** in ***non-*****pregnant patient** (**Folic acid** 2 mg/day ***should be*** taken with **Sulfasalazine**).
- **Antibiotics**; ***short courses*** of **Metronidazole** (not in 1st trimester) are ***safe*** for use ***during*** **pregnancy** & **breastfeeding** (**Ciprofloxacin** is ***not recommended***).
- **Immunosuppressive drugs**; **Azathioprine** and **Mercaptopurine** may be ***associated with*** **fetal deformities** in humans and are classified as ***pregnancy*** **category D**.
- **Methotrexate** ***should not*** be **used** ***during*** **pregnancy**, *known as* **abortifacient** (**category X**).
- **TNF-α Inhibitors**; **Infliximab**, **Adalimumab**, **Golimumab** & **Certolizumab** are **category B**.
- **Natalizumab** is a ***pregnancy*** **category C** and **Vedolizumab** is a ***pregnancy*** **category B**.

➤ Guidelines:-

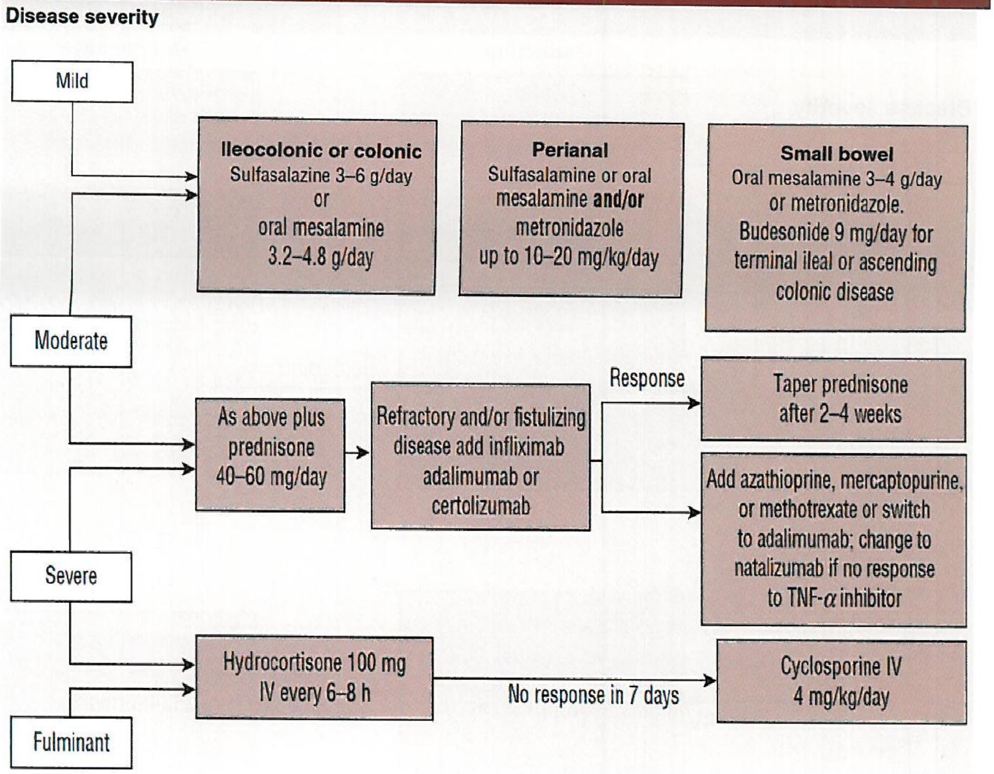
Ulcerative Colitis


Induction
Maintenance
Disease severity
Mild
Moderate
Severe
Fulminant
Distal
Topical sulfasalazine or mesalamine (preferred) or oral aminosalicylates or topical corticosteroids or oral mesalamine + topical mesalamine combination
Remission
Reduce oral mesalamine or sulfasalazine dose by one-half, or mesalamine enema 4 g every 1–2 days, or suppository 1 g every 1–2 days
Colitis
Sulfasalazine 4–6 g/day or oral mesalamine 2–4.8 g/day
Remission
Reduce sulfasalazine or mesalamine dose up to 2 g/days
Sulfasalazine 4–6 g/day or oral mesalamine 3.2–4.8 g/day PLUS prednisone 40–60 mg/day
Remission
Taper prednisone, then after 1–2 mo reduce sulfasalazine or mesalamine dose to those listed above
Inadequate or no response
Add azathioprine, mercaptopurine, or infliximab
Hydrocortisone IV 100 mg every 6–8 h
Remission
Change to prednisone
No response in 5–7 days
Cyclosporine IV 4 mg/kg/day
Reintroduce sulfasalazine or mesalamine, add azathioprine, mercaptopurine, or infliximab, attempt to withdraw steroids after 1–2 mo
Remission
Maintenance dose of sulfasalazine

- In *refractory* distal induction; **40-60 mg** of *oral* **Prednisone** or **Infliximab** as **5 mg/kg** IV at weeks 0, 2 and 6 can be used.
- ***Oral* Mesalamine + *topical* Mesalamine *combination more effective*** *than* **either agent *alone*.**
- In *refractory* distal maintenance; **Azathioprine**, **6-MP**, **Infliximab** or **Adalimumab** may be necessary if patients do not respond to **aminosalicylates therapy**.
- **Oral Budesonide** can be used as alternative first-line therapy **distal induction**.
- **Patients *should not be* treated *with* long-term steroids** for **maintenance therapy**.

R; Kornbluth A, Sachar DB. Ulcerative practice guidelines in adults. American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 2010;105:501-23. Algorithm edited from Dipiro pharmacotherapy.

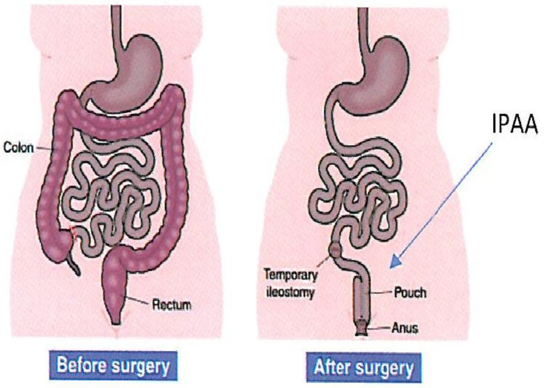
Crohn's Disease


Disease severity
Mild
Ileocolonic or colonic
Sulfasalazine 3–6 g/day
or
oral mesalamine
3.2–4.8 g/day
Perianal
Sulfasalamine or oral
mesalamine and/or
metronidazole
up to 10–20 mg/kg/day
Small bowel
Oral mesalamine 3–4 g/day
or metronidazole.
Budesonide 9 mg/day for
terminal ileal or ascending
colonic disease
Moderate
As above plus
prednisone
40–60 mg/day
Refractory and/or fistulizing
disease add infliximab
adalimumab or
certolizumab
Response
Taper prednisone
after 2–4 weeks
Add azathioprine, mercaptopurine,
or methotrexate or switch
to adalimumab; change to
natalizumab if no response
to TNF-α inhibitor
Severe
Hydrocortisone 100 mg
IV every 6–8 h
No response in 7 days
Cyclosporine IV
4 mg/kg/day
Fulminant

R; Lichtenstein GR, Hanauer SB, Sandborn WJ, The Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's Disease in Adults. Am J Gastroenterol 2009;104:465–483. algorithm from Dipiro pharmacotherapy.

➢ Surgery:-

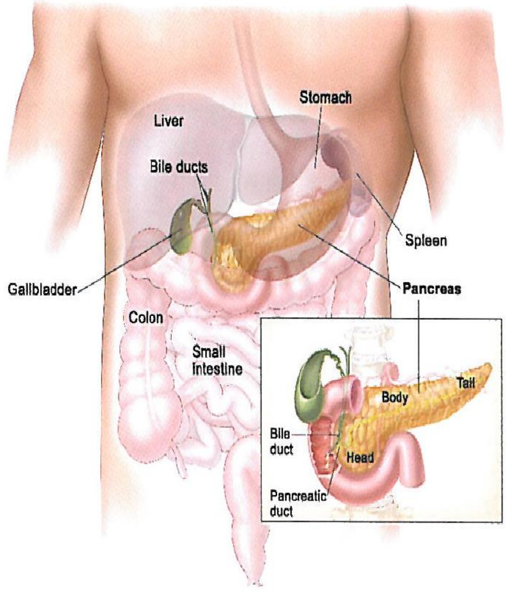
- **Ulcerative Colitis**;
  - **Proctocolectomy**; is the surgical removal of the rectum and all or part of the colon. In most cases, this involves a procedure called **ileal pouch/anal anastomosis (IPAA)**.
  - **IPAA**; is a surgical procedure that is used to restore gastrointestinal continuity after surgical removal of the colon and rectum.


Colon
Rectum
Before surgery
IPAA
Temporary ileostomy
Pouch
Anus
After surgery

- **Crohn's Disease**;
  - Up to 50% of people with Crohn's disease will require at least one surgery, however, surgery does not cure Crohn's disease, during surgery, removes of damaged portion of digestive tract and then reconnects the healthy sections. The benefits of surgery for Crohn's disease are usually temporary. The disease often recurs, frequently near the reconnected tissue.
  - **Strictureplasty**; is a surgical procedure performed to alleviate bowel narrowing due to scar tissue that has built up in the intestinal wall from Crohn's disease.
  - **Bowel resection** (**Enterectomy**); is a surgical procedure in which a part of bowel is removed.

Pancreatitis

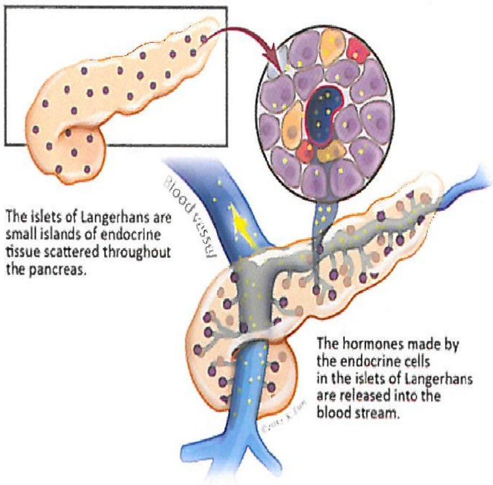
➢ Overview:-



- **Pancreas**; is the **large organ** *behind* the **stomach** that *produces* **digestive enzymes**.
- **Pancreatitis**; is ***inflammation*** of the **pancreas**.
- **Two** ***main types***; **acute pancreatitis** (lasts for days) & **chronic pancreatitis** (over many years).
- ***Most common*** **signs** and **symptoms**; **pain** (upper abdomen), **nausea** and **vomiting**.
- **Pain** is often ***goes into*** the **back** and is ***usually*** severe.
- ***Most common*** **causes** of **acute pancreatitis**; **gallstones** and ***heavy*** **alcohol** ***use***.
- ***Globally***; in **2013** *about* **17 million cases** of **pancreatitis** *occurred*, **123,000 deaths**.

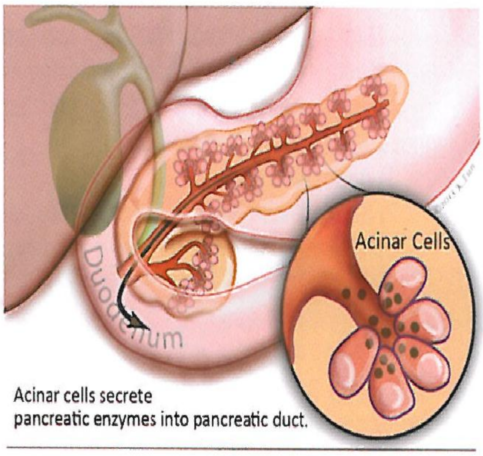
➢ Physiology;-

- **Pancreas Function**; The **pancreas** ***contain*** **two type** of **cells**;
  1) **Exocrine cells**; ***produce*** **enzymes** (**pancreatic juice**) to help in **digestion of food**, **pancreatic juice** ***secreted directly into*** the **duodenum** (first part of the small intestine).
  2) **Endocrine cells**; ***release*** **hormones**, such as **insulin** and **glucagon**, into *directly* ***into*** **blood stream** (endocrine) to ***control*** **blood glucose** ***levels***.



The islets of Langerhans are small islands of endocrine tissue scattered throughout the pancreas.

The hormones made by the endocrine cells in the islets of Langerhans are released into the blood stream.



Acinar cells secrete pancreatic enzymes into pancreatic duct.

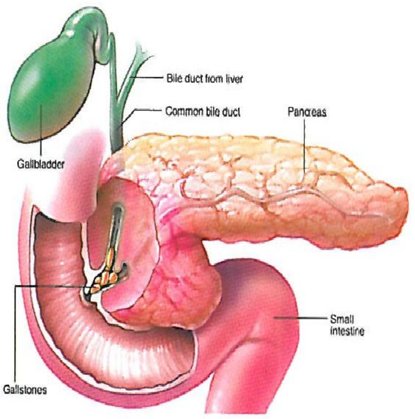
- **Pancreatic juice** are help in **protein**, **fat** and **carbohydrate** ***metabolism***, *contains*;

Trypsinogen	- Is the precursor form of Trypsin. - Trypsin function; hydrolysis of proteins (Proteolysis).
Chymotrypsinogen	- Is the precursor form of Chymotrypsin. - Chymotrypsin function; hydrolysis of proteins (Proteolysis).
Elastase	- Hydrolysis of proteins (Proteolysis).
Carboxypeptidase	- Hydrolysis of proteins (Proteolysis).
Pancreatic Lipase	- Hydrolysis of fats (lipids).
Nuclease	- Hydrolysis of nucleic acid.
Pancreatic Amylase	- Hydrolysis of carbohydrates.

➤ **Classifications:-**

Acute Pancreatitis

- ***Definition***; **Inflammation** in the **pancreas *ranging from* mild** to **severe, painful** and at ***times* deadly**.
- ***Failure***; ***loss of* exocrine function** and ***usually* reversible**.
- **Typical symptoms**; **Abdominal pain, nausea, vomiting, jaundice** and **fever**.
- **Phases**;
  1) **Early** (within 1 week): **systemic inflammatory response syndrome** (**SIRS**) or **organ damage**;
     - **SIRS**; is an inflammatory state affecting the whole body, *characterized by* 2 or more of the following;
       - Temperature; <36 °C or >38 °C.
       - Heart rate; > 90 beats per minute.
       - Respiratory rate; > 20 breaths per minute; or arterial partial pressure of CO_2 < 32 mmHg.
       - Abnormal white blood cell count.
  2) **Late** (more than 1 week): **local complications**; necrosis, hemorrhage, pseudocyst, abscess & infection.
- **Systemic complications**; **SIRS**, **acute respiratory distress syndrome**, **shock** and **organ failure**.
- **Main Causes**;



1) ***Long-term* alcohol abuse**.
2) **Gallstones** (obstruction).
3) **Drugs**;
   - **Didanosine** - **Asparaginase**.
   - **Azathioprine** - **Mercaptopurine**.
   - **Valproic acid** - **Diuretics** (**furosemide**, **HCTZ**).
   - **Exenatide** - **Sitagliptin**.
   - **Mesalamine** - **Sulfasalazine**.
   - **Estrogens** - **Pentamidine**.
   - **Trimethoprim/sulfamethoxazole** - **Tetracycline**.
4) Post–endoscopic retrograde cholangiopancreatography.
5) Hypertriglyceridemia (generally greater than 1000 mg/dL).
6) Idiopathic.
7) Structural abnormalities.
8) Toxins (scorpion venom).
9) Trauma.
10) Ischemia.

- **Severity** (Atlanta Symposium Criteria);
  - **Mild**: ***Absence* of organ failure** or **local complications**.
  - **Moderately severe**: **Local complications** or ***transient* organ failure** (<48 hours).
  - **Severe**: ***Persistent* organ failure** >48 hours.
- **Diagnosis**; **two** or **more** of the ***following***;
  1) **Abdominal pain**.
  2) **Serum lipase** (more than 3 times the upper limit of normal; ULN).
  3) **Abdominal ultrasonography** and **computed tomography** (**CT**) scan to evaluate pancreas.

Chronic Pancreatitis

- ***Definition***; *Characterized by* ***irreversible* structural** and **functional *loss*** of **pancreatic function** *caused by* ***long-standing* inflammation** and ***repeated* injury**.
- ***Failure***; ***irreversible* loss** of ***both* exocrine** and **endocrine function**.
- **Typical symptoms**; **chronic abdominal pain**, **steatorrhea**, **weight loss**, **jaundice** and **hyperglycemia**.
- **Complications**; **pseudocysts**, **calcification**, **ascites** and **biliary stricture**.
- **Risk factors**; based on **M-ANNHEIM** Classification;
  - **M** = Multiple risk factors.
  - **A** = Alcohol consumption.
  - **N** = Nicotine.
  - **N** = Nutritional factors (high fat and protein, hyperlipidemia).
  - **H** = Hereditary factors.
  - **E** = Efferent duct factors.
  - **I** = Immunologic factors.
  - **M** = Miscellaneous and rare factors (includes drugs).
- **Diagnosis**;

1) **Signs** and **symptoms**.
2) **Serum lipase** may be ***normal***; **hyperglycemia** and ***low* albumin** or **prealbumin** may also be present.
3) **CT scan** may ***reveal*** **pancreatic calcification** or **pseudocyst**.

➢ Treatment Strategies:-

Acute Pancreatitis

- Treatment is *largely* **supportive**;

1) **Remove** or **treat underlying cause** *if possible*.

2) **Rehydration therapy**; **IV fluids**; *typically* **lactated Ringer's** 250–500 mL/hour of (treat electrolyte disturbances; hypokalemia, hypocalcemia, hyperglycemia).

3) **Pain Management**; **IV narcotics** (*avoid* **Meperidine**; cause **spasm** of **sphincter** of **Oddi**).

4 **Antiemetics**; **IV Ondansetron**, **Prochlorperazine** or **Promethazine**.

5) **Nutrition**;

- If **mild pancreatitis**; **Oral feeding** can be **resumed** *if* **no vomiting** is present.
- If **severe pancreatitis**; **Enteral nutrition** to *prevent* **infectious complications**.

6) **Antibiotics**: In general, not recommended for routine prophylaxis in severe pancreatitis.

- If **infected necrosis**; **Carbapenems**, **Fluoroquinolones** or **Metronidazole** may be useful.

7) **Endoscopic retrograde cholangiopancreatography**; may be needed for cholangitis or gallstone pancreatitis (this is often followed by cholecystectomy to prevent future episodes).

R; American College of Gastroenterology. Practice guidelines: management of acute pancreatitis. Am J Gastroenterol 2013;108:1400-1.

Chronic Pancreatitis

- Treatment is *largely* **symptomatic**;

1) **Abstinence from alcohol** is *essential*.

2) **Pain management**;

- ***Combination*** of **non-narcotic** and **narcotic analgesics** (*long-acting* **Morphine**, **Oxycodone**, or transdermal **Fentanyl**) in ***combination with*** **pancreatic enzyme replacement**.
- ***Avoid*** **Acetaminophen** (if long-term alcohol use).

3) **Antiemetics**; Oral **Ondansetron**, **Prochlorperazine**, or **Promethazine**.

4) **Nutrition**;

- **Goals**; ***Maximize*** **caloric intake** and **weight gain** and ***reduce*** **steatorrhea**.
- ***May need*** *more* **frequent**, **lower-fat meals** and **fat-soluble vitamin** ***supplementation***.
- ***Long-term*** **enteral** or **parenteral nutrition** *may be* **required**.

5) **Pancreatic Enzyme Replacement Therapy (PERT)**; *see next* page.

➢ Pancreatic Enzyme Replacement Therapy (PERT):-

- ***Exocrine* pancreatic insufficiency** is ***most commonly*** *caused by* **cystic fibrosis, chronic pancreatitis** or **pancreatic resection.**
- *If* **secretion** of **pancreatic enzymes** *below* **10%** of **normal**; **fat** and **protein *digestion*** is ***impaired*** and can lead to **steatorrhea, azotorrhea, vitamin malabsorption** and **weight loss.**
- The **Pancreatic Enzyme Products** (**PEPs**) or **Pancrelipase** ***used in*** **PERT** are *extracts of* **porcine pancreas** that contain ***all*** **3 pancreatic enzymes** (**amylase, protease** and **lipase**) in ***varying proportions***, are ***used for*** **pancreatic enzyme insufficiency.**
- The are **6 PEPs** have been ***approved*** by the **US FDA**;

Pancreatic Enzyme Products (PEPs) or Pancrelipase

Brand	Lipase (units)	Amylase (units)	Protease (units)	Formulation
Creon®	3000	15,000	9500	Capsules with enteric-coated microspheres
	6000	30,000	19,000	
	12,000	60,000	36,000	
	24,000	120,000	76,000	
	36,000	180,000	114,000	
Viokace®	10,440	39,150	39,150	Immediate-release tablet
	20,880	78,300	78,300	
Pertzye®	8000	30,250	28,750	Capsules with enteric-coated microspheres
	16,000	28,750	57,500	
Zenpep®	3000	16,000	10,000	Capsules with enteric-coated beads
	5000	27,000	17,000	
	10,000	55,000	34,000	
	15,000	82,000	51,000	
	20,000	109,000	68,000	
	25,000	136,000	85,000	
	40,000	218,000	136,000	
Ultresa®	13,800	27,600	27,600	Capsules with enteric-coated mini-tablets
	20,700	41,400	41,400	
	23,000	46,000	46,000	
Pancreaze®	2600	10,850	6200	Capsules with enteric-coated micro-tablets
	4200	17,500	10,000	
	10,500	43,750	25,000	
	16,800	70,000	40,000	
	21,000	61,000	37,000	

- ***Dosing***; based on **lipase content** (units) in the product;
  - *Initial*; 500 units/kg/meal.
  - *Dose range*, 500-2500 units/kg/meal.
  - *Maximum dose*; 10,000 units/kg/day.
  - *Usually adult doses*; 30,000–40,000 units/meal, with one-half dose for snacks.
- ***Administration***; orally before or during meal.
- ***Dose monitoring***; ***increased*** in **weight gain** and ***decreased*** in **steatorrhea.**
- ***May need*** to ***add*** **proton pump inhibitors (PPIs)**; *if* **maximal response** is ***not seen.***
- ***Side effects***;
  - **Nausea** or **abdominal cramping.**
  - **Allergy** in patients with *pork allergy.*
  - **Hyperuricosuria, hyperuricemia.**
  - **Fibrosing colonopathy** (generally seen with doses greater than 10,000 units/kg/day)
- ***Pregnancy***; **category C.**

Gallstones

- **Bile** is a *complex* of **fluid** *containing* **water, electrolytes** and ***organic molecules*** *including* **bile acids, cholesterol, phospholipids** and **bilirubin.**
- *Bile Function*; - **Bile acids,** ***help for*** **digestion** and **absorption** of **fats** and **fat-soluble vitamins** in the **small intestine** (*by acting as a surfactant that emulsifies them into micelles*).
  - *Many* **waste products**, *including* **bilirubin**, are *eliminated from* the **body** by ***secretion*** into **bile** and *elimination in* **feces.**
- **Gall bladder** *stores* and *concentrates* **bile** and **cholesterol** is *soluble* in **bile.**
- **Gallstone** (**Cholelithiasis**); is a ***stone formed within*** **gallbladder**, *about* **80%** of **patients** are *asymptomatic*.
- **Gallstones**, *most of which* are **composed** *predominantly of* **cholesterol.**
- **Gallstones** *develop* when **bile** *contains too much* **cholesterol** and ***not enough*** **bile salts.**
- *Common Symptoms*; **biliary colic** (**crampy pain**; ***right*** **upper** **abdominal pain**, *usually* ***after*** **heavy meals** and *lasts* **1-4 hours**), *more than* **5 hours → Complication.**

METRIC 1
2
3
4

- *Complications signs*; **biliary colic** *more than* **5 hours, fever,** *persistent* **tachycardia, hypotension** and **jaundice** (yellowish skin).
- **Complication**; **cholecystitis, cholangitis** and **acute pancreatitis.**
- **Surgery**; *rapid* **treatment** of **complications** is **cholecystectomy** (**gallbladder** *remove*).
- *Medical treatments* of **asymptomatic gallstones** is **oral bile salt** (**Ursodeoxycholic acid**);

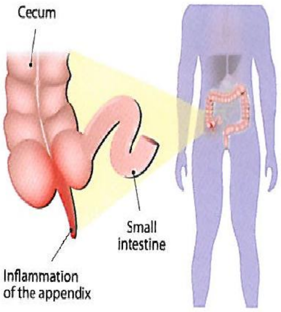
Ursodeoxycholic Acid or Ursodiol (Ursofalk®)

- **Ursodeoxycholic Acid** (**UDCA**) or **Ursodiol** is a ***naturally occurring*** **bile acid** found in *small quantities* in *normal* **human bile** and in ***larger quantities*** in the **bile** of *certain species* of **bears.**
- *Mechanisms*; 1) **Ursodiol** *regulate* **cholesterol** by; * *Reducing* **intestinal cholesterol** *absorption.*
  * *Reducing* **hepatic cholesterol** *synthesis* and *secretion.*
  2) **Ursodiol** is a **hydrophilic bile acid** that *solubilizes* **cholesterol** and *promotes* its **dispersion** in **aqueous fluids,** *reducing* **viscosity** and *improving* **bile flow.**
  - *From 1 and 2, results*; **Ursodiol** *reduces* **cholestasis,** *prevents* **formation** and *promotes* **dissolution** of **cholesterol-containing gallstones.**
- *Indications*; **Cholelithiasis, Primary Biliary Cholangitis (PBC), Cholestasis** (slowing or stopping of bile flow) in **cystic fibrosis, newborn infants** and **pregnant women** (relieve itching).
- **Chenodeoxycholic Acid** (**Chenodiol**) is an ***epimer of*** **Ursodeoxycholic Acid,** ***but*** have ***potential*** **hepatotoxicity** and ***poor*** **response.**

Rowachol®

- **Rowachol®** ***contains*** **essential oils** (**Pinene, Camphene, Cineol, Menthone, Menthol, Borneol**) that ***may help*** to ***dissolve*** or ***break up*** **cholesterol-based gallstones.**

Appendicitis



- **Appendicitis** is ***inflammation*** of the **appendix.**
- **Appendix** is a **tube** ***of*** **tissue** that ***extends from*** **large intestine.**
- There is ***no accurate*** **function** of **appendix** and we ***can*** **live *without* it.**
- **Appendicitis symptoms**; ***right*** **lower** **abdominal pain, nausea, vomiting** and *decreased* **appetite.**
- *Severe complications*; **ruptured appendix;** ***painful inflammation***, **sepsis** (pus-filled abscess) and can be **fatal.**
- *All cases* of **appendicitis** are treated as **emergencies,** ***requiring*** **surgery** (**appendectomy**).
- **IV antibiotics** are used to ***delay*** or ***avoid*** **the onset of sepsis.**